(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 January 2002 (17.01.2002)

PCT

(10) International Publication Number
WO 02/04452 A2

(51) International Patent Classification[7]: C07D 473/00

(21) International Application Number: PCT/US01/21526

(22) International Filing Date: 6 July 2001 (06.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/216,844 7 July 2000 (07.07.2000) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/04452 A2

(54) Title: METHODS FOR TREATMENT OF DISEASE-INDUCED PERIPHERAL NEUROPATHY AND RELATED CONDITIONS

(57) Abstract: A method of treating disease-induced peripheral neuropathy comprises administering to a patient with disease-induced peripheral neuropathy an effective quantity of a purine derivative or analogue, a tetrahydroindolone derivative or analogue, or a pyrimidine derivative or analogue. If the compound is a purine derivative, the purine moiety can be guanine or hypoxanthine. The compound can induce peripheral nerve sprouting through the action of a neurotrophic factor such as nerve growth factor (NGF) without the occurrence of hyperalgesia. The peripheral nerve sprouting can be nociceptive nerve sprouting. The disease-induced peripheral neuropathy can be diabetic neuropathy or disease-induced peripheral neuropathy with another basis.

METHODS FOR TREATMENT OF DISEASE-INDUCED PERIPHERAL NEUROPATHY AND RELATED CONDITIONS

CROSS-REFERENCES

This application claims priority from Provisional Application Serial No. 60/216,844, filed July 7, 2000 by Jack Diamond and Alvin J. Glasky, and entitled "Methods for Treatment of Peripheral Neuropathy and Related Conditions with Bifunctional Purine Analogues," which is incorporated herein in its entirety by this reference.

BACKGROUND OF THE INVENTION

This invention is directed to methods for treatment of disease-induced peripheral neuropathy and related conditions, particularly with purine derivatives or analogues, tetrahydroindolone derivatives or analogues, or pyrimidine derivatives or analogues.

Although methods have improved for the treatment of diabetes and its consequences, diabetic neuropathy is still an extremely serious problem. Diabetic neuropathy can be defined as a demonstrable disorder, either clinically evident or subclinical, that occurs in the setting of diabetes mellitus without other causes for peripheral neuropathy. The neuropathic disorder includes manifestations in the somatic and/or autonomic parts of the peripheral nervous system. Diabetic neuropathy often is associated with damage to the nerves just under the skin leading to one or more of the following conditions: numbness and tingling of fingers, hands, toes, and feet; weakness in hands and feet; or pain and/or burning sensation in hands and feet. Nerve damage as the result of peripheral neuropathy can also lead to problems with the GI tract, heart, and sexual organs, causing indigestion, diarrhea or constipation, dizziness, bladder infections, and impotence.

Diabetic neuropathy is one example of disease-induced peripheral neuropathy, which has other causes. Similar neuropathies can occur in conditions such as acromegaly, hypothyroidism, AIDS, leprosy, Lyme disease, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, periarteritis nodosa, Wegener's granulomatosis, cranial arteritis, and sarcoidosis, among other conditions.

More than 15% of the 13 million diabetic patients in the United States suffer symptomatic disturbances to the nervous system. Significant clinical neuropathy can

develop within the first 10 years after diagnosis of diabetes and the risk of developing neuropathy increases the longer a person has diabetes. Although in most cases (30-40%) there are no symptoms, up to 60% of patients with diabetes have some form of neuropathy. Diabetic neuropathy appears to be more common in smokers, people over 40, and those who have had problems controlling their blood glucose levels.

There are currently no drugs on the market for the treatment of diabetic neuropathy. There are some drugs in trials or awaiting trials, including alond (zopolrestat; Pfizer), zenarestat (Fujisawa), pregabalin (Warner-Lambert), timcodar dimesylate (Vertex), the NMDA antagonist memantine (Merz), neurulin (Cortec), and an IGF-II product (Aurogen).

Other approaches are being tried or being considered, including aldose reductase inhibitors, which are thought to inhibit the increased flux through the polyol pathway caused by high blood glucose, mimicking the effect of improved glycemic control, nerve growth factor, alpha-lipoic acid, gamma-linolenic acid as a food supplement, insulin-like growth factor hormones, immunoglobulin, myo-inositol, or aminoguanidine.

However, there is still a substantial need for an improved treatment for diabetic neuropathy, particularly a treatment that can actually slow or reverse the degeneration of the nerves involved without inducing hyperalgesia.

Therefore, there exists a need for improved methods for treating diabetic neuropathy as well as other disease-induced peripheral neuropathies. There is a particular need for methods that can stimulate nerve growth or regeneration, particularly without inducing hyperalgesia.

SUMMARY

One embodiment of the present invention is a method of treating disease-induced peripheral neuropathy comprising administering to a patient with peripheral neuropathy an effective quantity of an effective quantity of a compound comprising: (1) a moiety A selected from the group consisting of a purine moiety, a purine analogue, a tetrahydroindolone moiety, a tetrahydroindolone analogue, a pyrimidine moiety, and a pyrimidine analogue; (2) a hydrocarbyl moiety L of 1 to 6 carbon atoms that is linked to the moiety A and that can be cyclic, with the hydrocarbyl moiety being optionally substituted with one or more substituents selected from the group consisting of lower alkyl, amino, hydroxy, lower alkoxy, lower alkylamino, lower alkylthio, and

oxo; and (3) a moiety B that is linked to the moiety L though a carbonyl group wherein B is –OZ or N(Y_1)-D, where Z is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, aralkyl, or heteroaralkyl; D is a moiety that promotes absorption of the compound; and Y_1 is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms, which can be N, O, or S.

The purine moiety can be selected from the group consisting of hypoxanthine and guanine, as well as other purine moieties. A number of purine derivatives suitable for use in methods according to the present invention are disclosed. A particularly preferred purine derivative is N-4-carboxyphenyl-3-(6-oxohydropurin-9-yl) propanamide. Preferably, the compound is capable of passing through the blood-brain barrier.

Typically, the administration of the compound induces peripheral nerve sprouting in the skin of the patient to whom the purine derivative is administered. The peripheral nerve sprouting can be nociceptive nerve sprouting. Typically, the nociceptive nerve sprouting is induced without the occurrence of hyperalgesia. Additionally, methods according to the present invention can prevent large and small sensory nerve dysfunction in diabetes.

The disease-induced peripheral neuropathy can be diabetic neuropathy or can be a neuropathy associated with the following conditions: acromegaly, hypothyroidism, AIDS, leprosy, Lyme disease, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, periarteritis nodosa, Wegener's granulomatosis, cranial arteritis, or sarcoidosis.

BRIEF DESCRIPTION OF THE DRAWINGS

The following invention will become better understood with reference to the specification, appended claims, and accompanying drawings, where:

Figure 1(a) is a sketch of maps of newly-isolated mDCN-T13 nerve fields, with the individual heat, pinch, and touch areas identified;

Figure 1(b) is a graph showing the effect of AIT-082 on sprouting of nociceptive nerve fibers;

Figure 2(a) is a graph showing the effect of AIT-082 on sprouting of heat-nociceptive nerve fibers;

Figure 2(b) is a graph showing the effect of AIT-082 on sprouting of mechano-nociceptive nerve fibers;

Figure 3 is a graph showing the effect of AIT-082 in reversing the inhibition of sprouting by anti-NGF antibody;

Figure 4 is a graph showing that AIT-082 does not cause hyperalgesia as measured by threshold temperature for foot withdrawal from a hot probe, threshold temperature for evoking the CTM reflex in dorsal skin; and the latency of foot withdrawal from a 49°C hot bath;

Figure 5 is a graph showing the effect of AIT-082 on sensory nerve conduction velocity in control and diabetic rats;

Figure 6 is a graph showing the effect of AIT-082 on thermal response latency in control and diabetic rats;

Figure 7 is a graph showing the effect of AIT-082 on formalin-induced foot flinching in control and diabetic rats; and

Figure 8 is a graph showing the effect of AIT-082 on formalin-induced foot flinches in diabetic rats, showing the effect in phases 1, Q, and 2a.

DESCRIPTION

We have discovered that the bifunctional purine derivative N-4-carboxyphenyl-3-(6-oxohydropurin-9-yl) propanamide (also known as AIT-082 and leteprinim potassium), which bypasses the blood-brain barrier, can act to induce peripheral nerve sprouting in the skin of adult rats. As detailed below in the Example, this activity may be attributable to upregulation of cutaneous nerve growth factor (NGF) levels induced by this bifunctional purine derivative, although Applicants do not intend to be bound by this theory. Moreover, this activity occurred without the induction of hyperalgesia. This property of acting to induce peripheral nerve sprouting, therefore, should also be possessed by other purine derivatives and analogues, tetrahydroindolone derivatives and analogues, and pyrimidine derivatives and analogues, as discussed below. Methods according to the present invention can prevent large and small sensory nerve dysfunction in diabetes.

The peripheral nerve sprouting can be nociceptive nerve sprouting. The nociceptive nerve sprouting can occur without the induction of hyperalgesia.

Typically, a compound useful in a method of the present invention is capable of bypassing the blood-brain barrier.

More specifically, as detailed below in the Example, systematically administered AIT-082 closely mimics the effects both of increased levels of endogenous NGF, and of exogenous NGF. The compound induces vigorous collateral sprouting, and the sprouting it induced was blocked by systemic anti-NGF treatment. The growth of such nerve tissue is evoked and maintained entirely by the increased levels of NGF in adjacent denervated skin. However, AIT-082 resembles more the effects of increased endogenous NGF than of exogenous NGF, because it did not induce hyperalgesia.

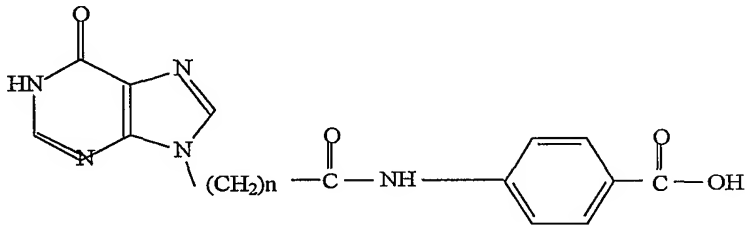
Accordingly, one aspect of the present invention is a method of treating disease-induced peripheral neuropathy comprising administering to a patient with disease-induced peripheral neuropathy an effective quantity of a compound, the compound comprising: (1) a moiety A selected from the group consisting of a purine moiety, a purine analogue, a tetrahydroindolone moiety, a tetrahydroindolone analogue, a pyrimidine moiety, and a pyrimidine analogue; (2) a hydrocarbyl moiety L of 1 to 6 carbon atoms that is linked to the moiety A and that can be cyclic, with the hydrocarbyl moiety being optionally substituted with one or more substituents selected from the group consisting of lower alkyl, amino, hydroxy, lower alkoxy, lower alkylamino, lower alkylthio, and oxo; and (3) a moiety B that is linked to the moiety L though a carbonyl group wherein B is –OZ or $N(Y_1)$-D, where Z is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, aralkyl, or heteroaralkyl; D is a moiety that promotes absorption of the compound having activity against a multi-drug transporter protein; and Y_1 is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms, which can be N, O, or S.

Typically, a compound useful in a method of the present invention is capable of passing through the blood-brain barrier.

In one preferred embodiment of methods according to the present invention, the moiety A is a purine moiety.

In one alternative, A is a substituted or unsubstituted hypoxanthine moiety. Typically, in this alternative, L has the structure $-(CH_2)_n$ where n is an integer from 1 to 6.

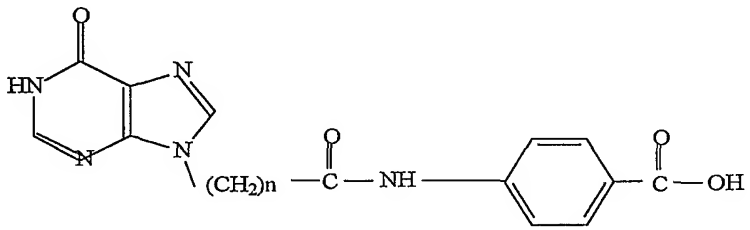
The compound having the activity against disease-induced peripheral neuropathy can be a compound of formula (I)



(I)

where n is an integer from 1 to 6 and R is hydrogen or lower alkyl or is a salt or prodrug ester of a compound of formula (I) wherein n is an integer from 1 to 6 and R is hydrogen or lower alkyl. Typically, the compound is a compound of formula (I) wherein n is an integer from 1 to 6 and R is hydrogen or lower alkyl. Typically, R is hydrogen, and the compound is N-4-[[3-(6-oxo-1,6-dihydropurin-9-yl)-1-oxopropyl] amino] benzoic acid, designated AIT-082. Alternatively, R is ethyl, and the compound is N-4-[[3-(6-oxo-1,6-dihydropurin-9-yl)-1-oxopropyl] amino] benzoic acid ethyl ester.

When the purine moiety is hypoxanthine, a preferred purine derivative is a compound of formula (I)

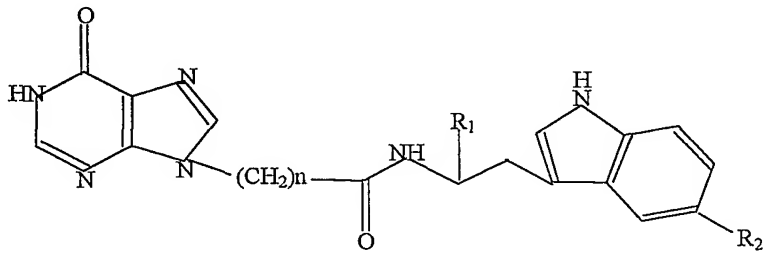


(I)

wherein n is an integer from 1 to 6 or of a salt or prodrug ester of formula (I) wherein n

is an integer from 1 to 6. Typically, the purine derivative is a compound of formula (I) wherein n is an integer from 1 to 6. Preferably, n is 2 and the compound is N-4-carboxyphenyl-3-(6-oxohydropurin-9-yl) propanamide, also known as AIT-082. The activity of this compound is described further in the Example.

Alternatively, the purine derivative can be a 9-substituted hypoxanthine derivative of formula (II)

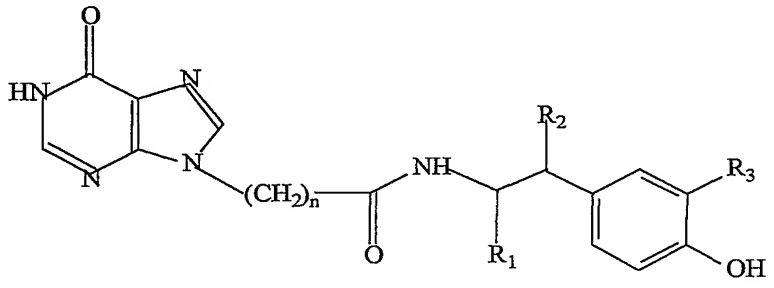


(II)

wherein n is a integer from 1 to 6, R_1 is selected from the group consisting of H, COOH, and $COOW_1$, where W_1 is selected from the group consisting of lower alkyl, amino, and lower alkylamino, and R_2 is selected from the group consisting of H and OH.

In this alternative, for one particularly preferred purine derivative, n is 2, R_1 is H and R_2 is OH and the purine derivative is N-(2-(5-hydroxyindol-3-yl))ethyl-3-(6-oxohydropurine-9-yl) propanamide. In this alternative, for another particularly preferred purine derivative, n is 2, R_1 is H and R_2 is H and the purine derivative is N-(2-indol-3-yl)ethyl-3-(6-oxohydropurin-9-yl) propanamide. In this alternative, for still another particularly preferred purine derivative, n is 2, R_1 is COOH, and R_2 is OH and the purine derivative is N-(1-carboxyl-(2-(5-hydroxyindol-3-yl))ethyl-3-(6-oxohydropurin-9-yl) propanamide.

As another alternative, the purine derivative can be a 9-substituted hypoxanthine derivative of formula (III)

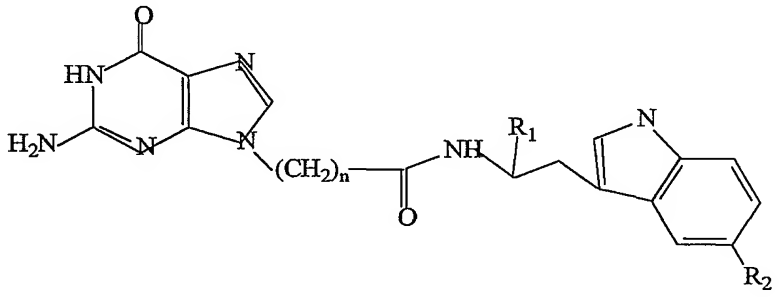


(III)

wherein n is an integer from 1 to 6, R_1 is selected from the group consisting of H, COOH, and $COOW_1$, wherein W_1 is selected from the group consisting of lower alkyl, amino, and lower alkylamino, R_2 is selected from the group consisting of H and OH, and R_3 is selected from the group consisting of H and OH.

In this alternative, for one particularly preferred purine derivative, n is 2, R_1 is H, R_2 is H, and R_3 is OH, and the purine derivative is N-(2-(3,4-dihydroxyphenyl))ethyl-3-(6-oxohydropurin-9-yl) propanamide. In this alternative, for another particularly preferred purine derivative, n is 2, R_1 is H, R_2 is OH, and R_3 is OH, and the purine derivative is N-(2-hydroxy-2-(3,4-dihydroxyphenyl))ethyl-3-(6-oxohydropurin-9-yl) propanamide. In this alternative, for still another particularly preferred purine derivative, n is 2, R_1 is COOH, R_2 is H, and R_3 is OH, and the purine derivative is N-(1-carboxyl-2-(3,4-dihydroxyphenyl))ethyl-3-(6-oxohydropurin-9-yl) propanamide.

When the purine moiety is guanine, one preferred purine derivative is a 9-substituted guanine derivative of formula (IV)



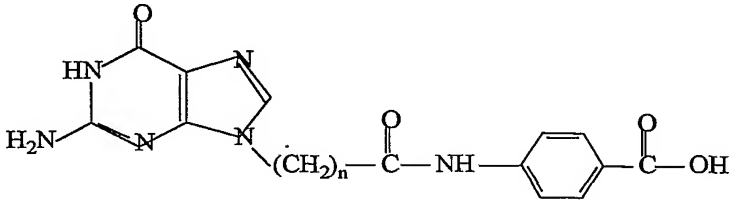
(IV)

wherein n is an integer from 1 to 6, R_1 is selected from the group consisting of H, COOH, and $COOW_1$, or W_1 is lower alkyl, amino, or lower alkylamino, and R_2 is selected from the group consisting of H and OH.

In this alternative, for one particularly preferred purine derivative, n is 2, R_1 is H, and R_2 is OH, and the purine derivative is N-(2-(5-hydroxindol-3-yl))ethyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide. In this alternative, for another particularly preferred purine derivative, n is 2, R_1 is H, and R_2 is H and the purine derivative is N-(2-(2-indol-3-yl)ethyl))-3-(2-amino-6-oxohydropurin-9-yl)) propanamide. In this alternative, for still another particularly preferred purine derivative, n is 2, R_1 is COOH, and R_2 is OH, and

the purine derivative is N-(1-carboxyl)-(2-(5-hydroxyindol-3-yl))ethyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

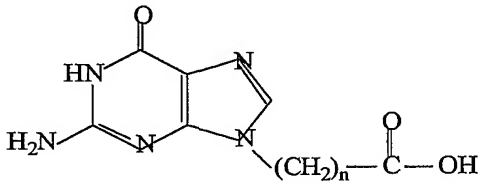
Alternatively, the purine derivative can be a 9-substituted guanine derivative of formula (V) wherein n is an integer from 1 to 6.



(V)

In this alternative, for one particularly preferred purine derivative, n is 2 and the compound is N-4-carboxyphenyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

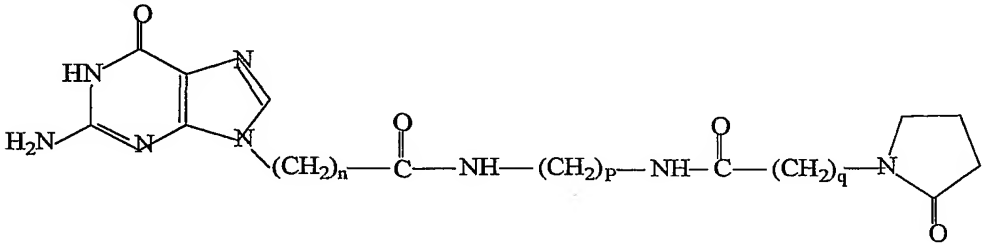
Alternatively, the purine derivative can be a 9-substituted guanine derivative of formula (VI) wherein n is an integer from 1 to 6.



(VI)

In this alternative, for one particularly preferred purine derivative, n is 2 and the compound is 3-(2-amino-6-oxohydropurine-9-yl) propanoric acid.

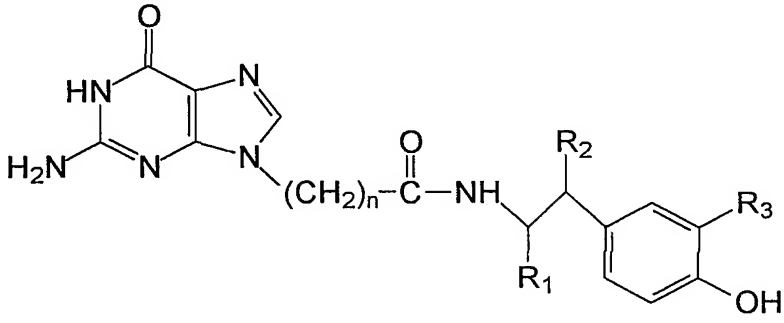
Alternatively, the purine derivative can be a 9-substituted guanine derivative of formula (VII) wherein n is an in integer from 1 to 6, p is an integer from 1 to 6, and q is an integer from 1 to 3.



(VII)

In this alternative, for one particularly preferred purine derivative, n is 2, p is 2, and q is 1, and the purine derivative is N-[2-[[2-(2-oxopyrrolidin-1-yl)-1-oxoethyl]amino]ethyl] propanamide.

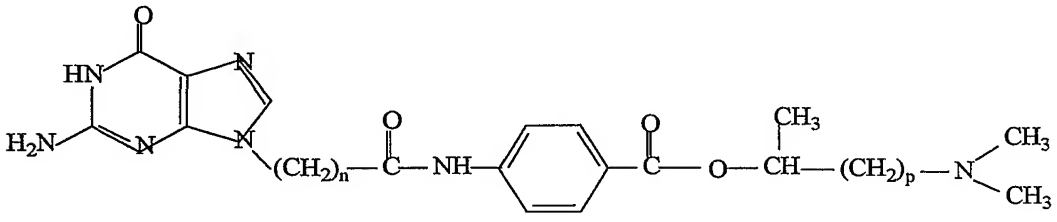
Alternatively, the purine derivative can be a 9-substituted guanine derivative of formula (VIII) wherein R_1 is selected from the group consisting of H, COOH, and $COOW_1$, where W_1 is selected from the group consisting of lower alkyl, amino, and lower alkylamino, R_2 is selected from the group consisting of H and OH, and R_3 is selected from the group consisting of H and OH.



(VIII)

In this alternative, for one particularly preferred purine derivative, n is 2, R_1 is H, R_2 is H, and R_3 is OH, and the purine derivative is N-(2-(3,4-dihydroxyphenyl)ethyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide. In this alternative, for another particularly preferred purine derivative, n is 2, R_1 is H, R_2 is OH, and R_3 is OH, and the purine derivative is N-(2-hydroxy-2-(3,4-dihydroxyphenyl)ethyl)-3-(2-amino-6-oxohydropurin-9-yl) propanamide. In this alternative, for still another particularly preferred purine derivative, n is 2, R_1 is COOH, R_2 is H, and R_3 is H and the compound is N-(1-carboxyl-2-(3,4-dihydroxyphenyl)ethyl)-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

Alternatively, the purine derivative can be a 9-substituted guanine derivative of formula (IX) wherein n is an integer from 1 to 6 and p is an integer from 1 to 3.



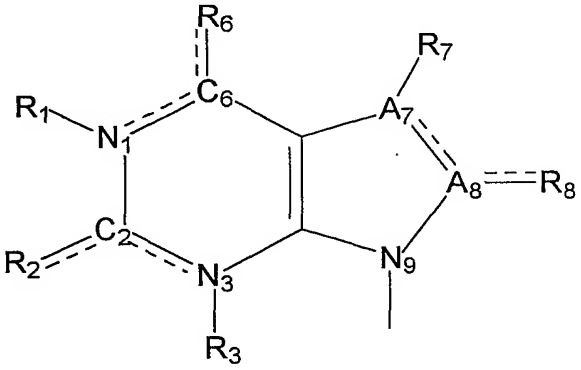
(IX)

In this alternative, for one particularly preferred purine derivative, n is 2, p is 1, and the compound is the 1-(dimethylamino)-2-propyl ester of N-4-carboxyphenyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

Other bifunctional hypoxanthine derivatives suitable for use in methods according to the present invention are disclosed in U.S. Patent No. 5,091,432 to Glasky, incorporated herein by this reference. Other bifunctional guanine derivatives

suitable for use in methods according to the present invention are disclosed in U.S. Patent Application No. 09/419,153, by Glasky et al., incorporated herein by this reference.

More generally, purine-based compounds suitable for use in methods according to the present invention are compounds in which A is a substituted or unsubstituted 9-atom bicyclic moiety in which the 5-membered ring has 1 to 3 nitrogen atoms, the bicyclic moiety having the structure of formula (X)



(X)

where:

(1) if the bond between N_1 and the bond between C_5 is a single bond, then the bond between C_6 and R_6 is a double bond, R_6 is O or S, and R_1 is hydrogen, alkyl, aralkyl, cycloalkyl, or heteroaralkyl;

(2) if the bond between N_1 and C_6 is a double bond, then the bond between C_6 and R_6 is a single bond, R_1 is not present, and R_6 is hydrogen, halo, amino, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(3) if the bond between C_2 and N_3 is a single bond, then the bond between C_2 and R_2 is a double bond, R_2 is O or S, and R_3 is hydrogen or alkyl;

(4) if the bond between C_2 and N_3 is a double bond, then the bond between C_2 is a single bond, R_3 is not present, and R_2 is hydrogen, alkyl, aralkyl, cycloalkyl, heteroaralkyl, halo, amino, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(5) A_7 and A_8 are C or N;

(a) if A_7 and A_8 are both C and the bond between A_7 and A_8 is a single bond, then the bond between A_8 and R_8 is two single bonds to two hydrogen atoms or is a double bond in which R_8 is O or S and R_7 is two hydrogen atoms;

(b) if A_7 and A_8 are both C and the bond between A_7 and A_8 is a double bond, then R_7 is hydrogen, the bond between A_8 and R_8 is a single bond and R_8 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(c) if A_7 and A_8 are both N, then the bond between A_7 and A_8 is a double bond, and R_7 and R_8 are not present;

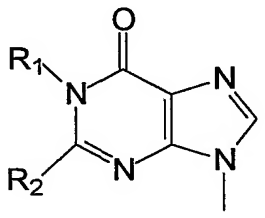
(d) if A_7 is C and A_8 is N, then the bond between A_7 and A_8 is a double bond, R_7 is hydrogen, and R_8 is not present;

(e) if A_7 is N, A_8 is C, and the bond between A_7 and A_8 is a double bond, then R_7 is not present, the bond between A_8 is a single bond, and R_8 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(f) if A_7 is N, A_8 is C, and the bond between A_7 and A_8 is a single bond, then R_7 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, the bond between A_8 and R_8 is a double bond, and R_8 is O or S; and

(6) N_9 is bonded to L; with the proviso that A does not have the structure of an unsubstituted guanine or hypoxanthine.

The purine moiety can be a purine moiety of formula (XI)



(XI)

in which:

(1) R_1 is selected from the group consisting of hydrogen, alkyl, aralkyl, cycloalkyl, and heteroaralkyl; and

(2) R_2 is selected from the group consisting of hydrogen, alkyl, aralkyl, cycloalkyl, heteroaralkyl, halo, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, arylkoxycarbonyl, heteroarylokoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroarylkylaminocarbonyl in which the alkyl portions could be cyclic and can contain from one to three heteroatoms which could be N, O, or S, with the proviso that both R_1 and R_2 are not hydrogen and that R_1 is not hydrogen when R_2 is amino.

The purine moiety of formula (XI) is a hypoxanthine or a guanine derivative but excludes unsubstituted hypoxanthine, in which R_1 and R_2 are hydrogen, and unsubstituted guanine, in which R_1 is hydrogen and R_2 is amino.

In one particularly preferred embodiment, R_1 is butyl and R_2 is hydrogen.

In another preferred embodiment, R_1 is benzyl and R_2 is hydrogen.

In another preferred embodiment, R_1 is dimethylaminoethyl and R_2 is hydrogen.

In another preferred embodiment, R_1 is cyclopentyl and R_2 is hydrogen.

In another preferred embodiment, R_1 is cyclohexylmethyl and R_2 is hydrogen.

In another preferred embodiment, R_1 is cyclopropylmethyl and R_2 is hydrogen.

In another preferred embodiment, R_1 is hydrogen and R_2 is phenyl.

In another preferred embodiment, R_1 is hydrogen and R_2 is trifluoromethyl.

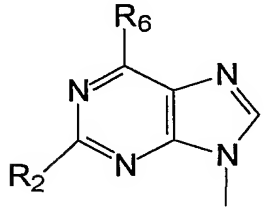
In another preferred embodiment, R_1 is hydrogen and R_2 is butyl.

In another preferred embodiment, R_1 is butyl and R_2 is butyl.

In another preferred embodiment, R_1 is hydrogen and R_2 is methyl.

In another preferred embodiment, R_1 is hydrogen and R_2 is phenylamino.

Alternatively, the purine moiety is a purine moiety of Formula (XII)



(XII)

in which:

(1) R_2 is selected from the group consisting of hydrogen, halo, amino, OQ_3, SQ_3, $NHNH_2$, $NHOQ_3$, NQ_3Q_4, or NHQ_3, where Q_3 and Q_4 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, and heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_3 and Q_4 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_3 where Y_3 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S; and

(2) R_6 is selected from the group consisting of hydrogen, halo, amino, OQ_5, SQ_5, $NHNH_2$, $NHOQ_5$, NQ_5Q_6, or NHQ_6, where Q_5 and Q_6 are alkyl, aralkyl,

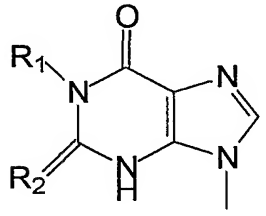
heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, and heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_5 and Q_6 are present together and are alkyl, they can be taken together to form a 5- or 6- membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, arylkoxycarbonyl, heteroarylkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S.

In one preferred example of this embodiment, R_2 is hydrogen and R_6 is $-NH_2$ or $-N(CH_3)_2$.

In another preferred example of this embodiment, R_2 is hydrogen and R_6 is Cl.

In yet another preferred example of this embodiment, R_2 is $-NH_2$ and R_6 is Cl.

In another alternative, the purine moiety is the purine moiety of Formula (XIII)



(XIII)

in which:

(1) R_1 is hydrogen, alkyl, aralkyl, cycloalkyl, or heteroaralkyl; and

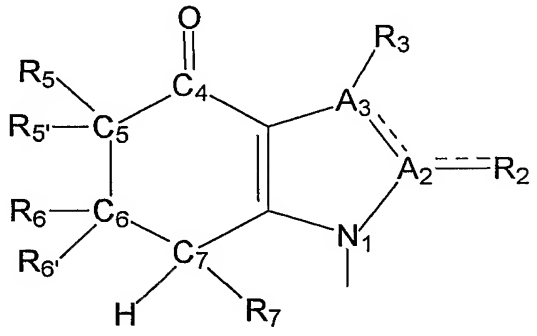
(2) R_2 is O or S.

Preferably, in this embodiment, R_1 is hydrogen and R_2 is O or S.

Particularly preferred purine-based compounds for use in methods according to the present invention include: (1) 4-[3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)propionylamino] benzoic acid ethyl ester; (2) 4-[3-(1-butyl-6-oxo-1,6-dihydropurin-9-yl)propionylamino] benzoic acid ethyl ester; (3) 4-[3-(1-methyl-6-oxo-1,6-dihydropurin-9-yl)propionylamino] benzoic acid ethyl ester; (4) 4-[3-(1-(2-dimethylaminoethyl)-6-oxo-1,6-dihydropurin-9-yl)propionylamino] benzoic acid ethyl ester; (5) 4-[3-(2,6-dioxo-1,2,3,6-tetrahydropurin-9-yl)propionylamino] benzoic acid ethyl ester; (6) 4-[3-(6-

methoxypurin-9-yl)propionylamino] benzoic acid ethyl ester; (7) 4-[3-(6-dimethylaminopurin-9-yl)propionylamino] benzoic acid ethyl ester; (8) 4-[3-(2-amino-6-chloropurin-9-yl)propionylamino] benzoic acid ethyl ester; (9) 4-[2-(6-oxo-2-thioxo-1,2,3,6-tetrahydropurin-9-yl)propionylamino]benzoic acid ethyl ester; (10) 4-[2-(2-butyl-6-oxo-1,6-dihydropurin-9-yl)propionylamino]benzoic acid ethyl ester; (11) 4-[2-(6-oxo-2-phenyl-1,6-dihydropurin-9-yl)propionylamino]benzoic acid ethyl ester; (12) 4-{[3-(6-chloropurin-9-yl)propionyl]methylamino} benzoic acid methyl ester; (13) 3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)-N-[3-(2-oxopyrrolidin-1-yl)propyl] propionamide; (14) 3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)-N-{2-[2-(2-oxopyrrolidin-1-yl)acetylamino]ethyl} propionamide; (15) N-3-(2-oxopyrrolidin-1-yl)propyl]-3-(6-oxo-2-thioxo-1,2,3,6-tetrahydropurin-9-yl) propionamide; and (16) 3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)-N-(3-morpholin-4-yl-propyl) propionamide.

In another alternative of methods according to the present invention, the compound is a tetrahydroindolone derivative or analogue where A is a 9-atom bicyclic moiety in which the 5-membered ring has one to three nitrogen atoms, the bicyclic moiety having the structure of formula (XIV)



(XIV)

where:

(1) N_1 is bonded to L;

(2) A_2 and A_3 are C or N;

(a) If A_2 and A_3 are both C and the bond between A_2 and A_3 is a single bond, then the bond between A_2 and R_2 is two single bonds, two hydrogen atoms or is a double bond in which R_2 is O or S and R_3 is two hydrogen atoms;

(b) If A_2 and A_3 are both C and the bond between A_2 and A_3 is a double bond, then R_3 is hydrogen, the bond between A_2 and R_2 is a single bond and R_2 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(c) If A_2 and A_3 are both N, then the bond between A_2 and A_3

is a double bond and R_2 and R_3 are not present;

(d) If A_2 is N and A_3 is C, then the bond between A_2 and A_3 is a double bond, R_2 is not present, and R_3 is hydrogen;

(e) If A_2 is C, A_3 is N, and the bond between A_2 and A_3 is a double bond, then R_3 is not present, the bond between A_2 and R_2 is a single bond, and R_2 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(f) If A_2 is C, A_3 is N, and the bond between A_2 and A_3 is a single bond, then R_3 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, or heteroaralkenyl, the bond between A_2 and R_2 is a double bond, and A_2 is O or S;

(3) R_5 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, NH_2, NHQ_1, NQ_1Q_2, OH, OQ_1, or SQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom, which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(4) $R_{5'}$ is hydrogen unless R_5 is alkyl, in which case R_5 is hydrogen or the same alkyl as R_5;

(5) R_5 and $R_{5'}$ can be taken together as a double bond to C_5, and can be O, S, NQ_3, or C which can be substituted with one or two groups R_5, where Q_3 is

alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

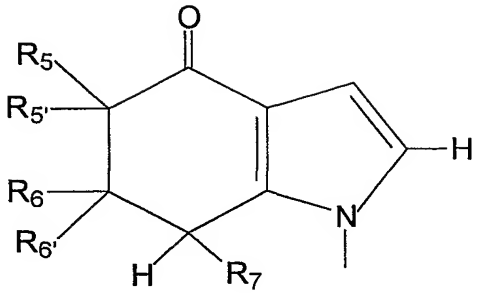
(6) R_6 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, NH_2, NHQ_4, NQ_4Q_5, OH, OQ_4, or SQ_4, where Q_4 and Q_5 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_4 and Q_5 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom, which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(7) $R_{6'}$ is hydrogen unless R_6 is alkyl, in which case $R_{6'}$ is hydrogen or the same alkyl as R_6;

(8) R_6 and $R_{6'}$ can be taken together as a double bond to C_6 and can be O, S, NQ_6, or C which can be substituted with one or two groups R_5, and where Q_6 is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S; and

(9) R_7 is hydrogen unless R_5 is alkyl and $R_{5'}$ is hydrogen, in which case R_7 is the same alkyl as R_5.

Typically, A is a tetrahydroindolone moiety. More typically, the tetrahydroindolone moiety is a tetrahydroindolone moiety of formula (XV)



(XV)

in which:

(1) R_5 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, NH_2, NH_1, NQ_1Q_2, OH, OQ_1, or SQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl, in which the alkyl portions can be cyclic and can contain from one to three heteroatoms which can be N, O, or S;

(2) $R_{5'}$ is hydrogen;

(3) R_6 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, NH_2, NHW_1, NQ_1Q_2, OH, OQ_1, or SQ_1, where Q_1 and Q_2 are aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl, in which the alkyl portions can be cyclic and can contain from one to three heteroatoms which can be N, O, or S and where W_1 is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from one to three heteroatoms which can be N, O, or S;

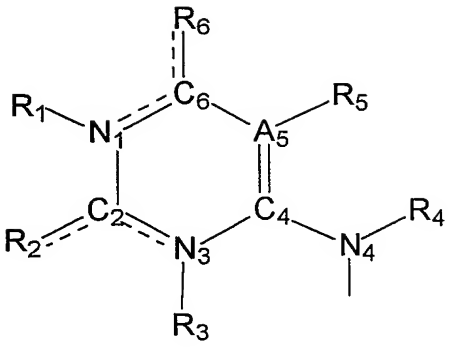
(4) $R_{6'}$ is hydrogen; and

(5) R_7 is hydrogen.

Typically, R_5, $R_{5'}$, R_6, $R_{6'}$, and R_7 are all hydrogen.

When A is a tetrahydroindolone moiety, preferred compounds are 4-[3-(4-oxo-4,5,6,7-tetrahydroindolon-1-yl) propionylamino] benzoic acid ethyl ester and 4-[3-(4-oxo-4,5,6,7-tetrahydroindolon-1-yl) propionylamino] benzoic acid.

In another alternative, the compound is a pyrimidine derivative or pyrimidine analogue. In this alternative, A is an amino-substituted 6-membered heterocyclic moiety of formula (XVI)



(XVI)

where:

(1) if the bond between N_1 and the bond between C_6 is a single bond, then the bond between C_6 and R_6 is a double bond, R_6 is O or S, and R_1 is hydrogen, alkyl, aralkyl, cycloalkyl, or heteroaralkyl;

(2) if the bond between N_1 and C_6 is a double bond, then the bond between C_6 and R_6 is a single bond, R_1 is not present, and R_6 is hydrogen, halo, amino, OH, OQ_1, SQ_1, $NHNH_2$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(3) if the bond between C_2 and N_3 is a single bond, then the bond between C_2 and R_2 is a double bond, R_2 is O or S, and R_3 is hydrogen or alkyl;

(4) if the bond between C_2 and N_3 is a double bond, then the bond between C_2 and R_2 is a single bond, R_3 is not present, and R_2 is hydrogen, alkyl, aralkyl, cycloalkyl, heteroaralkyl, halo, amino, OH, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl,

heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_3, where Y_3 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(5) R_4 is hydrogen, alkyl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl;

(6) A_5 is carbon or nitrogen;

(7) if A_5 is nitrogen, then R_5 is not present;

(8) if A_5 is carbon, then R_5 is hydrogen, amino, alkyl, alkoxy, halo, nitro, aryl, cyano, alkenyl, or alkaryl;

(9) if R_5 and R_6 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S; and

(10) N_4 is bonded to L.

Typically, A_5 is carbon and the 6-membered heterocyclic moiety is a pyrimidine moiety.

When A is a pyrimidine moiety, in one alternative, R_2 is O and R_3 is hydrogen. In this alternative, the pyrimidine moiety can be cytosine, thymine, uracil, 3-methyluracil, 3-methylthymine, 4-methylcytosine, 5-methylcytosine, 5-hydroxymethylcytosine, 5-hydroxyuracil, 5-carboxymethyluracil, or 5-hydroxymethyluracil.

In another alternative, R_2 is S and R_3 is hydrogen. In this alternative, the pyrimidine moiety can be 2-thiouracil, 5-methylamino-2-thiouracil, 5-methyl-2-thiouracil, or 2-thiocytosine.

In still another alternative, R_2 is amino and the bond between C_2 and N_3 is a double bond. In this alternative, the pyrimidine moiety can be 2-aminopyrimidinone or 2-amino-4-chloropyrimidine.

In still another alternative, R_2 is hydrogen and the bond between C_2 and N_3 is a double bond. In this alternative, the pyrimidine moiety can be 4-chloropyrimidine, 5-amino-4-chloropyrimidine, 4-chloro-5-methylpyrimidine, 4-chloro-5-hydroxymethylpyrimidine, or 4-chloro-5-carboxymethylpyrimidine.

In still another alternative, R_1 is hydrogen, methyl, or ethyl, R_5 is hydrogen, methyl, or ethyl, and R_6 is O. In this alternative, the pyrimidine moiety can be pyrimidinone.

Particularly preferred pyrimidine compounds include: 4-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester; 4-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester; 4-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester; 4-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid; 4-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid; 4-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid; 3-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester; 3-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester; 3-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester; 3-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid; 3-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid; and 3-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid.

In accordance with the present invention, and as used herein, the following terms, when appearing alone or as part of a moiety including other atoms or groups, are defined with the following meanings, unless explicitly stated otherwise. In

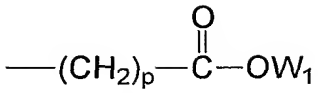
addition, all groups described herein can be optionally substituted unless such substitution is excluded. The term "alkyl," as used herein at all occurrences, refers to saturated aliphatic groups including straight-chain, branched-chain, and cyclic groups, all of which can be optionally substituted. Preferred alkyl groups contain 1 to 10 carbon atoms. Suitable alkyl groups include methyl, ethyl, and the like, and can be optionally substituted. The term "alkenyl," as used herein at all occurrences, refers to unsaturated groups which contain at least one carbon-carbon double bond and includes straight-chain, branched-chain, and cyclic groups, all of which can be optionally substituted. Preferable alkenyl groups have 2 to 10 carbon atoms. The term "alkoxy" refers to the ether –O—alkyl, where alkyl is defined as as above. The term "aryl" refers to aromatic groups which have at least one ring having a conjugated π-electron system and includes carbocyclic aryl and biaryl, both of which may be optionally substituted. Preferred aryl groups have 6 to 10 carbon atoms. The term "aralkyl" refers to an alkyl group substituted with an aryl group. Suitable aralkyl groups include benzyl and the like; these groups can be optionally substituted. The term "aralkenyl" refers to an alkenyl group substituted with an aryl group. The term "heteroaryl" refers to carbon-containing 5-14 membered cyclic unsaturated radicals containing one, two, three, or four O, N, or S heteroatoms and having 6, 10, or 14 π-electrons delocalized in one or more rings, e.g., pyridine, oxazole, indole, thiazole, isoxazole, pyrazole, pyrrole, each of which can be optionally substituted as discussed above. The term "sulfonyl" refers to the group -S(O_2)-. The term "alkanoyl" refers to the group -C(O)Rg, where Rg is alkyl. The term "aroyl" refers to the group -C(O)Rg, where Rg is aryl. Similar compound radicals involving a carbonyl group and other groups are defined by analogy. The term "aminocarbonyl" refers to the group –NHC(O)-. The term "oxycarbonyl" refers to the group –OC(O)-. The term "heteroaralkyl" refers to an alkyl group substituted with a heteroaryl group. Similarly, the term "heteroaralkenyl" refers to an alkenyl group substituted with a heteroaryl group. As used herein, the term "lower," in reference to an alkyl or the alkyl portion of an another group including alkyl, is defined as a group containing one to six carbon atoms. The term "optionally substituted" refers to one or more substituents that can be lower alkyl, aryl, amino, hydroxy, lower alkoxy, aryloxy, lower alkylamino, arylamino, lower alkylthio, arylthio, or oxo, in some cases, other groups can be included, such as cyano, acetoxy, or halo. The term "halo" refers generally to fluoro, chloro, bromo, or iodo; more typically, "halo" refers to chloro.

As indicated above, the linker L is a hydrocarbyl moiety of 1 to 6 carbon atoms that can be cyclic, with the hydrocarbyl moiety being optionally substituted with one or more substituents selected from the group consisting of lower alkyl, amino, hydroxy, lower alkoxy, lower alkylamino, lower alkylthio, and oxo. Preferably, the linker L has the structure $-(CH_2)_n-$ wherein n is an integer from 1 to 6. As detailed below, for most preferred embodiments of compounds useful in methods according to the present invention, a preferred linker has n equal to 2 or 3.

The moiety B is either: (i) –OZ, where Z is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, aralkyl, or heteroaralkyl; or (ii) $N(Y_1)$-D, where D is a moiety that promotes absorption of the compound, and Y_1 is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, which, when taken with D, can form a cyclic 5- or 6-membered saturated ring which can contain one other heteroatom which can be O, N, or S, of which N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S. Typically, Y_1 is hydrogen. Where the moiety B is –OZ, the moiety B is a carboxylic acid or carboxylic acid or ester. Typically, where B is a carboxylic acid ester, the moiety Z is a lower alkyl, such as methyl, ethyl, butyl, propyl, or isopropyl.

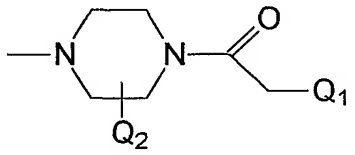
In one alternative, the moiety D, as described above, is a moiety having at least one polar, charged, or hydrogen-bond-forming group to improve the metabolic and bioavailability properties of the compound. The moiety D can be, but is not limited to, a moiety with physiological or biological activity such as nootropic activity. In one alternative, the moiety D can be a moiety containing at least one carboxyl, carboxamide, carboxyl ester, or carbonyl function. In another alternative, the moiety D can be a moiety containing at least one hydroxyl, primary amino, secondary amino, tertiary amino, sulfhydryl, or sulfonamidyl function. The moiety D can be cyclic or acyclic. Preferred examples of the moiety D are described below.

When the moiety D is a cyclic or acyclic moiety containing at least one carbonyl, carboxamide, carboxyl ester, or carbonyl function, in one preferred example, D is a carboxylic acid or carboxylic acid ester with the structure



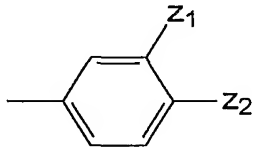
wherein p is an integer from 1 to 6 and W_1 is selected from the group consisting of hydrogen and lower alkyl. Typically, if W_1 is lower alkyl, it is methyl, ethyl, propyl, butyl, or isobutyl. Typically, p is 3. Typically, W_1 is hydrogen or ethyl.

In another preferred example, D and Y_1 are taken together to form a piperazine derivative as described in D. Manetti et al., "Molecular Simplification of 1,4-Diazabicyclo[4.3.0]nonan-9-ones Gives Piperazine Derivatives That Maintain High Nootropic Activity," J. Med. Chem. 43: 4499-4507 ("Manetti et al. (2000)"). B is an analogue of structure



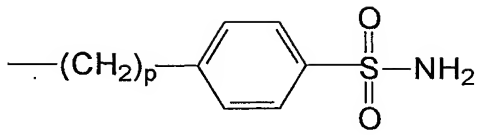
wherein Q_1 is hydrogen, methyl, ethyl, butyl, or propyl, Q_2 is hydrogen or methyl, where, if Q_2 is methyl, it can be located at either of the two possible positions in the piperazine ring.

In another preferred example, D has the structure



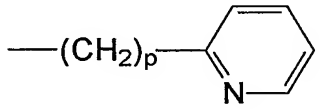
where one of Z_1 and Z_2 is hydrogen, and the other of Z_1 and Z_2 is –COOH or -$COOW_1$, wherein W_1 is alkyl. Typically, W_1 is selected from the group consisting of methyl, ethyl, propyl, butyl, and isobutyl. Either of Z_1 or Z_2 can be hydrogen. When Z_1 is hydrogen and Z_2 is –COOH, the moiety B is *p*-aminobenzoic acid (PABA). When Z_1 is –COOH and Z_2 is hydrogen, the moiety B is *m*-aminobenzoic acid (MABA). When Z_1 is hydrogen and Z_2 is –$COOW_1$, the moiety B is an ester of *p*-aminobenzoic acid (PABA). When Z_1 is –$COOW_1$ and Z_2 is hydrogen, the moiety B is an ester of *m*-aminobenzoic acid (MABA). Typically, these esters are ethyl esters.

When the moiety D is a moiety that contains at least one hydroxyl, primary amino, secondary amino, tertiary amino, sulfhydryl, or sufonamidyl function, in one preferred example, D is a phenylsulfonamidyl moiety of structure



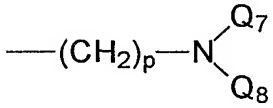
wherein p is an integer from 0 to 6. Typically, p is 2.

In another preferred example, D is an alkylpyridyl moiety of structure



wherein p is an integer from 1 to 6. Typically, p is 1.

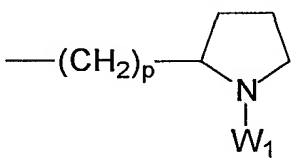
In another preferred example, D is a dialkylaminoalkyl moiety of the structure



wherein p is an integer from 1 to 6 and Q_7 and Q_8 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5 or 6 member ring which may contain 1 other heteroatom which can be N, O, or S, of which the N may be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S.

Where Q_7 and Q_8 can be taken together to form a five or six member ring, the ring is typically pyrrolidine, piperidine, or morpholine. The pyrrolidine ring can be optionally substituted with oxo. The piperidine ring can be optionally substituted with methyl or ethyl. Typically, p is 2 or 3.

In another preferred example, D is an alkylpyrrolidine moiety of the structure



wherein p is an integer from 1 to 6 and W_1 is selected from the group consisting of methyl, ethyl, and propyl. Typically, W_1 is methyl. Typically, p is 2.

Preferably, a compound useful in methods according to the present invention has a log P of from about 1 to about 4 in order to optimize bioavailability and CNS penetration of the compound.

As detailed below in the Example, compounds used in methods according to the present invention are believed to exert their activity through the upregulation of neurotrophic factor synthesis. The upregulation of neurotrophic factor synthesis can involve one or more of these neurotrophic factors: NGF, NT-3, BDNF, and NT-4/5.

Exemplary studies and treatments were performed as discussed below using various dosages and routes of administration of selected exemplary compounds representative of compositions that are effective with the methods of the present invention. Of course, those skilled in the art will recognize that the present invention is not specifically limited to the particular compositions, dosages or routes of administration detailed below.

Depending upon the particular needs of the individual subject involved, the compositions used in the present invention may be administered in various doses to provide effective treatment concentrations based upon the teachings of the present invention. What constitutes an effective amount of the selected composition will vary based upon such factors including the activity of the selected compound, the physiological characteristics of the subject, the extent and nature of the subject's disease or condition and the method of administration. Exemplary treatment concentrations which have proven effective in modifying neural activity range from less than 1 μM to concentrations of 500 mM or more. Generally, initial doses will be modified to determine the optimum dosage for treatment of the particular mammalian subject. The compositions may be administered using a number of different routes including orally, topically, transdermally, intraperitoneal injection or intravenous injection directly into the bloodstream. Of course, effective amounts of the compounds may also be administered through injection into the cerebrospinal fluid or infusion directly into the brain, if desired.

The methods of the present invention may be effected using compounds administered to a mammalian subject either alone or in combination as a pharmaceutical formulation. Further, the compounds may be combined with pharmaceutically acceptable excipients and carrier materials such as inert solid

diluents, aqueous solutions or non-toxic organic solvents. If desired, these pharmaceutical formulations may also contain preservatives and stabilizing agents and the like, as well as minor amounts of auxiliary substances such as wetting or emulsifying agents, as well as pH buffering agents and the like which enhance the effectiveness of the active ingredient. The pharmaceutically acceptable carrier can be chosen from those generally known in the art, including, but not limited to, human serum albumin, ion exchangers, dextrose, alumina, lecithin, buffer substances such as phosphate, glycine, sorbic acid, potassium sorbate, propylene glycol, polyethylene glycol, and salts or electrolytes such as protamine sulfate, sodium chloride, or potassium chloride. Other carriers can be used.

Liquid compositions can also contain liquid phases either in addition to or to the exclusion of water. Examples of such additional liquid phases are glycerin, vegetable oils such as cottonseed oil, organic esters such as ethyl oleate, and water-oil emulsions.

The compositions can be made into aerosol formations (i.e., they can be "nebulized") to be administered via inhalation. Aerosol formulations can be placed into pressurized acceptable propellants, such as dichloromethane, propane, or nitrogen. Other suitable propellants are known in the art.

Formulations suitable for parenteral administration, such as, for example, by intravenous, intramuscular, intradermal, and subcutaneous routes, include aqueous and non-aqueous, isotonic sterile injection solutions. These can contain antioxidants, buffers, preservatives, bacteriostatic agents, and solutes that render the formulation isotonic with the blood of the particular recipient. Alternatively, these formulations can be aqueous or non-aqueous sterile suspensions that can include suspending agents, thickening agents, solubilizers, stabilizers, and preservatives. Compositions suitable for use in methods according to the present invention can be administered, for example, by intravenous infusion, orally, topically, intraperitoneally, intravesically, or intrathecally. Formulations of compounds suitable for use in methods according to the present invention can be presented in unit-dose or multi-dose sealed containers, in physical forms such as ampules or vials.

The disease-induced peripheral neuropathy to be treated can be diabetic neuropathy or can be a peripheral neuropathy arising as the result of another condition, such as, but not limited to, acromegaly, hypothyroidism, AIDS, leprosy, Lyme disease, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's

syndrome, periarteritis nodosa, Wegener's granulomatosis, cranial arteritis, and sarcoidosis.

Although Applicants do not intend to be bound by this theory, the beneficial effects of bifunctional purine derivatives such as AIT-082 may depend on generalized trophic and NGF-sensitive mechanisms and not merely on the induction of sprouting. These trophic effects may boost the capacity of NGF-sensitive neurons to respond to still unknown regeneration factors other than NGF itself. For example, it is likely that CGRP and Substance P expression increases with treatment with AIT-082 or other bifunctional purine derivatives. Methods according to the present invention also can prevent large and small sensory nerve dysfunction in diabetes.

The invention is illustrated by the following Examples. These Examples are presented for illustration only and is not intended to limit the invention.

EXAMPLE 1

Administration of the Bifunctional Purine Derivative N-4-Carboxyphenyl-3-(6-Oxohydropurin-9-yl) Propanamide Induces Nociceptive Nerve Sprouting

The purpose of this study was to evaluate the effects of AIT-082 in the peripheral nervous system (PNS), focusing on well-characterized nerve growth factor (NGF)-dependent collateral sprouting of nociceptive nerves into denervated skin and within partially denervated skin (Nixon et al., 1984; Doucette and Diamond 1987). The induction and maintenance of this sprouting are brought about by endogenous NGF (Diamond et al., 1992), which increases in nerve-depleted skin both because of an increased NGF mRNA expression (Mearow et al., 1993), and because NGF is no longer taken up into eliminated nerve endings (Korsching and Thoenen, 1985). Systemically injected NGF induces sprouting in normal skin, enhances an on-going sprouting into adjacent denervated skin, and can restore a sprouting reduced by concomitant anti-NGF treatment (Diamond et al., 1992; Pertens et al., 1999). The clinical utility of exogenous NGF is severely limited because it causes hyperalgesia (Lewin et al., 1993, 1994). AIT-082 may up-regulate the expression of neurotrophic factors, including NGF. Thus we chose to examine the extent to which AIT-082 injections would mimic exogenous NGF, and if so, to discover if it's effects were due to a direct action on neurons, or via an AIT-082-induced up-regulation of endogenous NGF. Given that AIT-082 might have therapeutic applications and that exogenous NGF causes hyperalgesia we also examined whether its systemic administration induces hyperalgesia.

METHODS

All the animal procedures used in these studies were approved by the Institutional Animal Research Ethics Board, and conform to NIH guidelines. In terminal experiments animals were sacrificed while anesthetized with sodium pentobarbitone, 45 mg/kg (injected intraperitoneally, or i.p.), which was used for all operative procedures and during electrophysiological recording sessions. The nociceptive field mappings were done using 35 mg/kg pentobarbitone, which allows the CTM reflex (see below) to be elicited while maintaining the anesthetic state.

"Isolation" of sensory fields: This procedure, the initial step in the study of collateral sprouting and was done as described in Diamond et al. (1992). Its purpose was to isolate the cutaneous innervation territory, or field, of a selected nerve within a vast surround of denervated back skin. The nerve used was the medial branch of the left dorsal cutaneous nerve (DCN), at segmental level T13 (mDCN-T13). The isolation of its field was achieved by surgically eliminating on the left side the 4 DCNs immediately rostral and caudal to DCN-T13 (respectively T9 -T12 and L1-L4), the lateral branch of DCN-T13, and the 4 lateral cutaneous nerves supplying the flank skin adjacent to the DCN-T13 territory.

Mapping of sensory fields: As described in Nixon et al. (1984) and Doucette and Diamond (1987), the borders of the isolated mechano-nociceptive and heat-nociceptive fields, subserved respectively by the Aδ and C fibers mDCN-T13, were determined by systematically applying across the skin forceps pinches (for mechano-nociception) and brief applications of a 60°C heat probe (for heat-nociception); the presence of nociceptive endings is indicated during these procedures when the stimuli elicit the "CTM reflex" response, a contraction of the underlying *cutaneus trunci* muscle, which causes a characteristic and easily recognized skin twitch (Theriault and Diamond, 1988). The low-threshold ("touch") fields were measured electrophysiologically as described by Jackson and Diamond (1984). The DCN-T13 was placed across bipolar platinum electrodes that fed into a preamplifier and thence to an oscilloscope and audio amplifier. Brushing innervated skin with a fine bristle generates impulses in the large myelinated Aβ axons, producing audible responses that disappear abruptly as the bristle crosses into denervated territory. The areas of the cutaneous territories of the three sensory modalities studied ("pinch", "heat" and "touch") were measured using the MCID image analysis system (Imaging Research, Inc., St. Catharines, Ontario, Canada).

Measurement of collateral sprouting: The collateral sprouting of pinch and heat fibers in the DCN-T13, and the axonal regeneration of these and of the touch (Aβ) axons which do not undergo collateral sprouting in adult animals (Jackson and Diamond, 1984; Yasargil et al., 1988) were measured by periodic field re-mappings. These re-mappings revealed the progressive expansion of the initially isolated mDCN-T13 nociceptive areas into the surrounding denervated skin as collateral sprouting proceeded (Nixon et al., 1984; Doucette and Diamond, 1987).

Detection of hyperalgesia: Nociceptive responses were studied in lightly restrained animals as described in Pertens et al. (1999), using the latency of foot withdrawal from a 49°C footbath, the temperature of the footbath at which withdrawal was initiated, and the heat thresholds for evoking the "CTM" reflex from back skin (see above). Hyperalgesia is defined here as a lowering of the threshold of a nociceptive stimulus required to produce a reflex response, and/or a reduction in the latency of that response.

Administration of AIT-082: AIT-082 was obtained from NeoTherapeutics Inc., Irvine, California, USA. A 50 mg/ml solution in sterile 0.9% NaCl was made up freshly every three days. The standard administration protocol was a daily i.p. injection of 50 mg/kg AIT-082. A limited dose-response study (not illustrated) confirmed that this treatment was well above threshold for inducing nociceptive sprouting, but below saturating levels for this response.

Preparation of NGF and its antiserum: The preparation and purification of nerve growth factor (2.5S NGF or 7S NGF) from male mouse salivary glands and of anti-NGF antiserum (anti-NGF) from adult sheep, and the evaluation of potency in functional assays, were done as described in detail in Diamond et al. (1992).

Administration of anti-NGF antiserum: Subcutaneous injections were made in the groin region (not the region of back skin under study). The "low", or "adequate", dose anti-NGF treatment referred to later had a biological titer of 1:3,300, and was used at 0.3 ml/250 gm; the "high" or "supramaximal" anti-NGF had a titer of 1:10,000 and was used at 0.5 ml/250 gm.

RESULTS

1. AIT-082 induces sensory nerve sprouting in normally innervated skin, but only of NGF sensitive fibers.

Here we report on whether AIT-082 would induce morphologically-demonstrable sprouting, and associated field expansions, within normally innervated

skin. Two groups of unoperated rats were injected daily with either AIT-082 (50 mg/kg) or saline for 20 days. The innervation territory of mDCN-T13 was then isolated in each animal, as explained in Methods, to allow measurement of the two nociceptive areas of innervation (the heat field and the pinch field) by behavioral mapping, and the touch field, subserved by the NGF-insensitive Aβ fibers (Diamond et al., 1987) by electrophysiological mapping. The results are shown in Figure 1a and 1b; the two nociceptive fields, pinch and heat, had expanded significantly in the animals receiving AIT-082 treatment, but the touch fields were unaffected.

2. AIT-082 enhances nociceptive sprouting into adjacent denervated skin.

This experiment examined whether the induction of sprouting by AIT-082 described above was additive to an on-going collateral sprouting into adjacent denervated skin. Immediately following the standard field isolation and mappings of the selected mDCN-T13 in two groups of rats, a daily regimen of AIT-082 injections was instituted in one group, with the second group receiving saline. The mappings were repeated every 3 or 4 days thereafter. Beginning at about 13 days post-isolation, an increased expansion of the nociceptive fields became apparent in the AIT-082 group relative to the expansions in the control group (Figure 2). Because field expansions are represented here as a ratio (field area at the selected time relative to the initial field area), a direct comparison between this data and that of Figure 1 is not possible. However, a comparison was achieved using the raw data that went to construct Figures 1 and 2; it showed that after 20 days of treatment, the amount by which the field expansions in the AIT-082 sprouting group exceeded the expansions in the controls was approximately equal to the expansion in field areas induced in unoperated animals after 20 days of AIT-082 treatment (shown in Figure 1).

3. AIT-082 rescues a sprouting blocked by a just-adequate anti-NGF treatment, but not one blocked by a supramaximal treatment.

The objective here was to discover how AIT-082-induced sprouting was affected by an anti-NGF treatment known to inhibit spontaneous collateral sprouting (Diamond et al., 1992). AIT-082 was administered daily throughout the period of a standard sprouting paradigm, exactly as in the experiment described in Figure 2, but in this instance anti-NGF was also administered daily. In one group of animals the anti-NGF dosage was selected to be just adequate to block collateral sprouting on its own, while in a second group the anti-NGF dosage was about 5-fold this "threshold" dose (see Methods). The pinch and heat fields were measured after 22 days in all the

animals. As seen in Figure 3, AIT-082 totally rescued the sprouting that would otherwise have been blocked by the threshold ("low") anti-NGF treatment, but sprouting continued to be absent in the animals receiving the "supra-threshold" ("high") anti-NGF treatment.

4. AIT-082 does not cause hyperalgesia.

Groups of unoperated animals that had received the standard AIT-082 administration that caused nociceptive field expansions like those shown in figure 1 were examined at various times for the presence of hyperalgesia. As seen in figure 4, a number of recognized tests for hyperalgesia failed to provide any evidence for the occurrence of this phenomenon at any time during or following a treatment by AIT-082 that induced sprouting.

DISCUSSION

AIT-082 promotes nociceptive sprouting by way of an up-regulation of endogenous NGF.

The present study shows firstly that systemically administered AIT-082 brings about a marked collateral sprouting of nociceptive nerves in adult rats, a sprouting normally driven entirely by skin-derived NGF (Diamond et al., 1992). However, AIT-082 does not evoke sprouting of the non-nociceptive Aβ sensory fibers, which are NGF-insensitive (Diamond et al., 1992). AIT-082 administration thus brings about a nociceptive hyper-innervation of the skin in unoperated animals, and enhances an on-going NGF-driven nociceptive sprouting into adjacent denervated skin. The absolute increase that AIT-082 produced in such an on-going sprouting was approximately equal to the amount of de novo sprouting (measured by the field expansion) it induced in the normally innervated skin of unoperated animals. In all these respects AIT-082 injections mimicked the effects of NGF injections (Diamond et al., 1992).

The second major finding is that the sprouting induced by AIT-082 is not achieved via a direct action on the nociceptive neurons, but is secondary to its action in up-regulating *endogenous* NGF levels. A block of spontaneous sprouting into adjacent denervated skin produced by a just-adequate anti-NGF treatment was completely reversed by administration of AIT-082, but AIT-082-induced sprouting was itself prevented when the anti-NGF dosage was increased approximately 5-fold.

Clinical implications of the present findings.

There is increasing evidence that deficient neurotrophic support, including that provided to cutaneous nerves by NGF, contributes to the pathogenesis of the most

common of peripheral neuropathies, diabetic neuropathy (Anand, 1996; Tomlinson et al., 1997), and indeed clinical trials of NGF as a treatment for this condition are already in progress (Apfel, 1998). Indirect support for this therapeutic approach comes from our earlier findings (Diamond et al., 1988; 1992) that chronic NGF-deprivation causes a shrinkage of nociceptive fields in the skin consistent with a "dying-back" neuropathy. AIT-082 administration, were it to induce endogenous NGF increases in the skin of diabetic individuals, could help protect NGF-sensitive neurons from the threat of diabetic neuropathy, without the hazard of hyperalgesia, as explained above.

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EXAMPLE 2

Administration of the Bifunctional Purine Derivative N-4-Carboxyphenyl-3-(6-Oxohydropurin-9-yl) Propanamide Prevents Sensory Nerve Dysfunction in Short-term Diabetic Rats

The aim of this study was to investigate the therapeutic potential of the purine analog AIT-082 in preventing nerve disorders that develop in diabetic rats.

Methods

All animal procedures were approved by the local animal subjects committee and were performed in accordance with NIH Guidelines on the Care and Use of Laboratory Animals.

Induction of diabetes: Female, adult, Sprague-Dawley rats (250-275g) were fasted overnight prior to the intraperitoneal injection of a freshly made solution of

streptozotocin in 0.9% saline to deliver a dose of 50 mg/kg body weight. Food was restored and animals left for 3 days before determination of glucose levels in a blood sample obtained by tail prick. Animals with blood glucose levels >15 mmol/l were considered diabetic and used in the study. Treatment with the AIT-082 began on the day that hyperglycemia was confirmed. Animals that did not present as diabetic at the first testing were re-dosed with streptazotocin and re-tested 3 days later. If they presented as diabetic then they were added to the study, if not they were omitted.

Blood and plasma glucose: Blood glucose was measured in freshly-obtained samples using a strip-operated reflectance meter (Glucostix and Glucocheck). At euthanasia, blood was collected by cardiac puncture and plasma extracted and stored at –20°C until subsequent measurement of glucose levels by spectrophotometric assay using the Trinder Kit (Sigma).

Nerve Conduction Velocity (NCV): Rats were anesthetized with halothane (4% in O_2 for induction, 2-3% for maintenance) and the sciatic nerve exposed via an incision in the flank followed by separation of underlying musculature by blunt dissection. A thermistor probe was placed adjacent to the nerve and the wound closed with a skin clamp and a second, rectal, probe was positioned. Nerve and rectal temperature was maintained at 37°C by a heating lamp and thermal pad connected to a temperature regulator and the thermistor probes. The nerve was stimulated (single 5v, 0.05ms square wave pulse) by fine needle electrodes placed at the sciatic notch and Achilles tendon and the evoked EMG recorded from the interosseus muscles via two fine needle electrodes and displayed on a digital storage oscilloscope. The distance between the two sites of stimulation was measured using surface calipers and NCV calculated as the latency between the $A\alpha/\beta$ wave peaks of the M wave (MNCV) or H wave (SNCV) divided by the distance between the two stimulation sites. NCV measurements were made in triplicate and the median used to represent the NCV. The thermistor probes were removed, the skin incision closed with wound clips and coated with Betadine and the animal withdrawn from halothane and monitored until it recovers consciousness. Rats were then returned to their cages with free access to food and water.

Thermal response latency: Rats were placed in an observation chamber on the surface (floor temperature 30°C) of a modified Hargreaves Apparatus (UARD, San Diego CA) and allowed to acclimate for 5 minutes. For measurement of thermal response latency, a heat source (delivering 4.5 amps to give a paw withdrawal latency

of approximately 10 seconds in control rats) was maneuvered underneath the hind paw. The heat source was turned on manually and a stop clock activated until it shut off automatically when the paw was moved (24 sec cut off time). The procedure was repeated 4 times on the same paw at 5 minute intervals and the median of values 2-4 used to represent the thermal response latency.

Formalin test: Rats were restrained manually and formalin (50µl of 0.2% solution) injected sub-dermally into the hindpaw dorsum. Rats were then placed in an observation chamber and flinching behaviors counted in 1 minute blocks every 5 minutes for 1 hour.

RESULTS

General physiology: Diabetic rats were hyperglycemic at the end of the study and AIT-082 did not affect plasma glucose levels in either control or diabetic rats. Diabetes caused loss of body weight and this was not altered by AIT-082.

SNCV (large sensory fiber): Diabetes reduced SNCV at weeks 4 and 8. AIT-082 had no effect in control rats or on the SNCV deficit at week 4. By week 8 there was a dose-dependent improvement of SNCV in diabetic rats treated with AIT-082 (Figure 5).

Thermal response latency (small sensory fiber): Diabetes produced a transient thermal hyperalgesia at week 4 that progressed to hypoalgesia by week 8. AIT-082 was without effect in control rats. In diabetic rats, AIT-082 dose-dependently prevented both hyperalgesia and hypoalgesia. The high dose (100 mg/kg) completely prevented both hyperalgesia at week 4 and hypoalgesia at week 8 (Figure 6).

Formalin test (primary sensory neurons with spinal modulation): Diabetes produced marked hyperalgesia during the formalin test (Figure 7). AIT-082 dose-dependently reduced formalin-evoked flinching in both control and diabetic rats. In diabetic rats the suppression of hyperalgesia was notable in phases 1, Q, and 2a (Figure 8). These data suggest a general analgesic property of AIT-082 rather than any selectivity for diabetes-induced hyperalgesia.

Conclusion: AIT-082 prevented large and small sensory nerve dysfunction in short-term diabetic rats

ADVANTAGES OF THE INVENTION

The present invention provides new methods for treating patients with peripheral neuropathy, including diabetic neuropathy and other types of peripheral

neuropathy, to induce peripheral nerve sprouting, which can include nociceptive nerve sprouting. These methods provide for nerve regeneration. These methods can be performed, at least in some alternatives, without inducing hyperalgesia. These methods can be combined with other treatments for peripheral neuropathy, including diabetic neuropathy, such as palliative measures for the relief of pain.

Although the present invention has been described in considerable detail, with reference to certain preferred versions thereof, other versions and embodiments are possible. Therefore, the scope of the invention is determined by the following claims.

WE CLAIM:

1. A method of treating disease-induced peripheral neuropathy comprising administering to a patient with disease-induced peripheral neuropathy an effective amount of a compound having activity against disease-induced peripheral neuropathy, the compound comprising: (1) a moiety A selected from the group consisting of a purine moiety, a purine analogue, a tetrahydroindolone moiety, a tetrahydroindolone analogue, a pyrimidine moiety, and a pyrimidine analogue; (2) a hydrocarbyl moiety L of 1 to 6 carbon atoms that is linked to the moiety A and that can be cyclic, with the hydrocarbyl moiety being optionally substituted with one or more substituents selected from the group consisting of lower alkyl, amino, hydroxy, lower alkoxy, lower alkylamino, lower alkylthio, and oxo; and (3) a moiety B that is linked to the moiety L wherein B is –OZ or $N(Y_1)$-D, where Z is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, aralkyl, or heteroaralkyl; D is a moiety that promotes absorption of the compound having activity against disease-induced neuropathy; and Y_1 is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms, which can be N, O, or S.

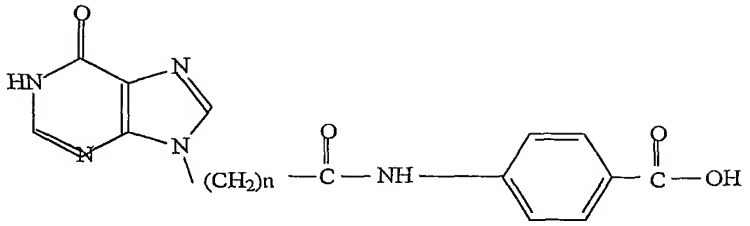
2. The method of claim 1 wherein the compound having activity against disease-induced neuropathy passes through the blood-brain barrier.

3. The method of claim 1 wherein A is a purine moiety.

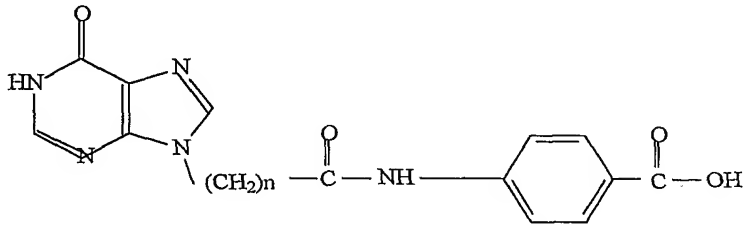
4. The method of claim 3 wherein A is a substituted or unsubstituted hypoxanthine moiety.

5. The method of claim 4 wherein L has the structure $–(CH_2)_n$-CONH- where n is an integer from 1 to 6.

6. The method of claim 5 wherein the compound having activity against disease-induced neuropathy is a compound of formula (I)



where n is an integer from 1 to 6 and R is hydrogen or lower alkyl or is a salt or prodrug ester of a compound of formula (I)



wherein n is an integer from 1 to 6 and R is hydrogen or lower alkyl.

7. The method of claim 6 wherein the compound having activity against disease-induced neuropathy is a compound of formula (I) wherein n is an integer from 1 to 6 and R is hydrogen or lower alkyl.

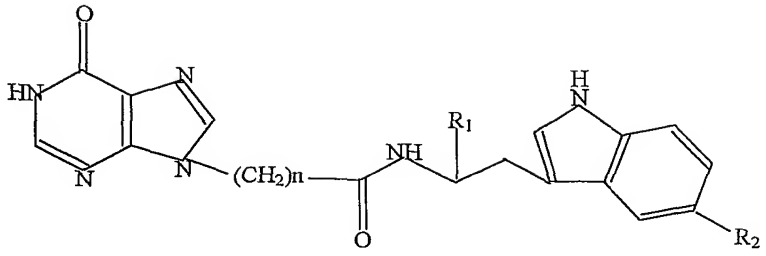
8. The method of claim 7 wherein R is hydrogen.

9. The method of claim 8 wherein n is 2 and the compound is N-4-[[3-(1,6-dihydro-6-oxo-purin-9-yl)-1-oxopropyl] amino] benzoic acid.

10. The method of claim 7 wherein R is ethyl.

11. The method of claim 10 wherein n is 2 and the compound is N-4-[[3-(1,6-dihydro-6-oxo-purin-9-yl)-1-oxopropyl] amino] benzoic acid ethyl ester.

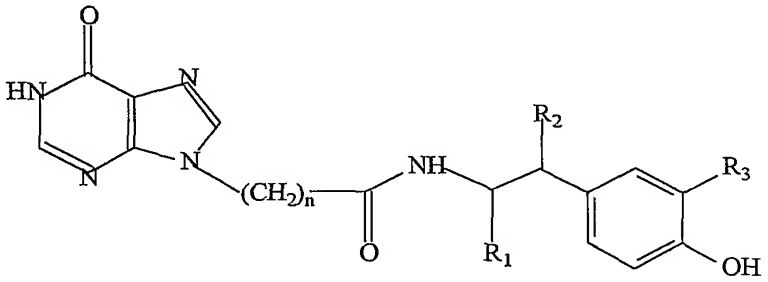
12. The method of claim 5 wherein the compound having activity against disease-induced neuropathy is a compound of formula (II)



wherein n is an integer from 1 to 6, R is selected from the group consisting of H, COOH, and $COOW_1$, wherein W_1 is selected from the group consisting of lower alkyl, amino, and lower alkylamino, and R_2 is selected from the group consisting of H and OH.

13. The method of claim 12 wherein n is 2.

14. The method of claim 5 wherein the compound having activity against disease-induced neuropathy is a compound of formula (III)



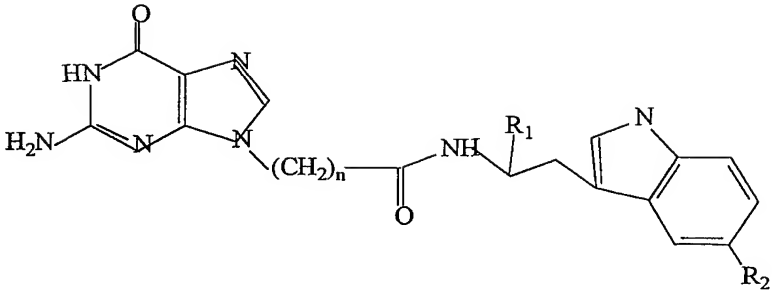
wherein n is an integer from 1 to 6, R_1 is selected from the group consisting of H, COOH, and $COOW_1$, wherein W_1 is selected from the group consisting of lower alkyl, amino, and lower alkylamino, R_2 is selected from the group consisting of H and OH, and R_3 is selected from the group consisting from the group consisting of H and OH.

15. The method of claim 14 wherein n is 2.

16. The method of claim 3 wherein A is a substituted or unsubstituted guanine moiety.

17. The method of claim 16 wherein L has the structure $-(CH_2)_n$-CONH- wherein n is an integer from 1 to 6.

18. The method of claim 17 wherein the compound having activity against disease-induced neuropathy is a compound of formula (IV)



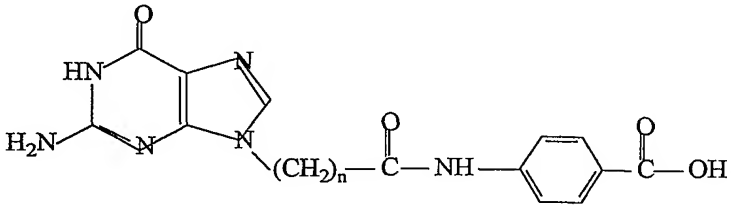
wherein n is an integer from 1 to 6, R_1 is selected from the group consisting of H, COOH, and $COOW_1$, wherein W_1 is selected from the group consisting of lower alkyl, amino, and lower alkylamino and R_2 is selected from the group consisting of H and OH.

19. The method of claim 18 wherein n is 2, R_1 is H, and R_2 is OH, and the compound is N-(2-(5-hydroxyindol-3-yl)) ethyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

20. The method of claim 18 wherein n is 2, R_1 is H, and R_2 is H, and the compound is N-(2-(2-indol-3-yl)ethyl))-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

21. The method of claim 18 wherein n is 2, R_1 is COOH, and R_2 is OH, and the compound is N-(1-carboxyl-(2-(5-hydroxyindol-3-yl)ethyl)-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

22. The method of claim 17 wherein the compound having activity against disease-induced neuropathy is a compound of formula (V)

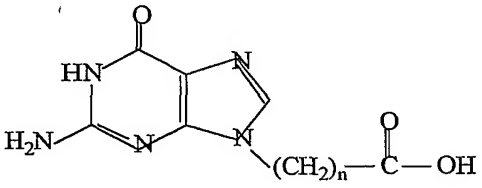


wherein n is an integer from 1 to 6 and R is selected from the group consisting of hydrogen and lower alkyl.

23. The method of claim 22 wherein n is 2, R is hydrogen, and the compound is N-4-carboxyphenyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

24. The method of claim 22 wherein n is 2, R is ethyl, and the compound is N-4-carboxyphenyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide ethyl ester.

25. The method of claim 17 wherein the compound having activity against disease-induced neuropathy is a compound of formula (VI)

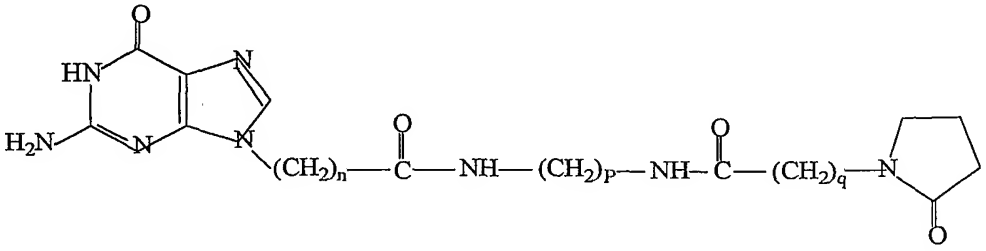


wherein n is an integer from 1 to 6 and R is selected from the group consisting of hydrogen and lower alkyl.

26. The method of claim 25 wherein n is 2, R is hydrogen, and the compound is 3-(2-amino-6-oxohydropurin-9-yl) propanoic acid.

27. The method of claim 25 wherein n is 2, R is ethyl, and the compound is 3-(2-amino-6-oxohydropurin-9-yl) propanoic acid ethyl ester.

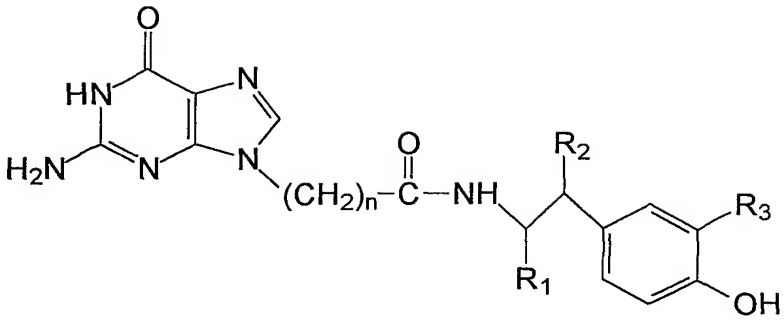
28. The method of claim 17 wherein the compound having activity against disease-induced neuropathy is a compound of formula (VII)



wherein n is an integer from 1 to 6, p is an integer from 1 to 6, and q is an integer from 1 to 3.

29. The method of claim 28 wherein n is 2, p is 2, and q is 1, and the compound is N-[2-[[2-(2-oxopyrrolidin-1-yl)-1-oxoethyl] amino] ethyl] propanamide.

30. The method of claim 17 wherein the compound having activity against disease-induced neuropathy is a compound of formula (VIII)



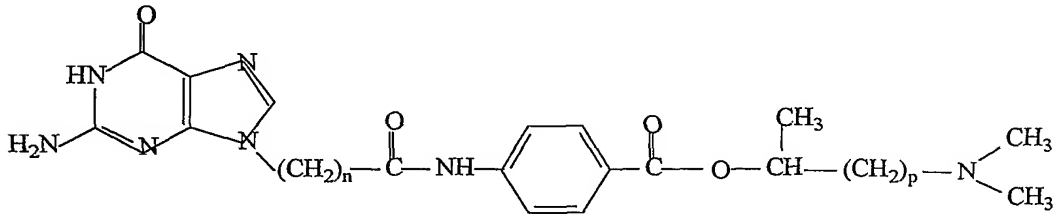
wherein n is an integer from 1 to 6, R_1 is selected from the group consisting of H, COOH, and $COOW_1$, wherein W_1 is selected from the group consisting of lower alkyl, amino, and lower alkylamino, R_2 is selected from the group consisting of H and OH, and R_3 is selected from the group consisting of H and OH.

31. The method of claim 30 wherein n is 2, R_1 is H, R_2 is H, and R_3 is OH, and the compound is N-(2-(3,4-dihydroxyphenyl)ethyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

32. The method of claim 30 wherein n is 2, R_1 is H, R_2 is OH, and R_3 is OH, and the compound is N-(2-hydroxy-2-(3,4-dihydroxyphenyl)ethyl)-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

33. The method of claim 30 wherein n is 2, R_1 is COOH, R_2 is H, and R_3 is H, and the compound is N-(1-carboxyl-2-(3,4-dihydroxyphenyl)ethyl)-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

34. The method of claim 16 wherein the compound having activity against disease-induced neuropathy is a compound of formula (IX)

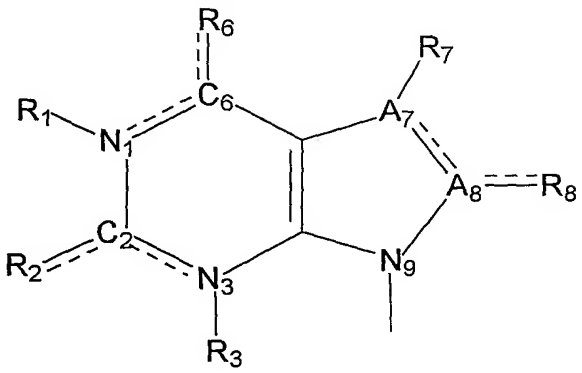


wherein n is an integer from 1 to 6 and p is an integer from 1 to 3.

35. The method of claim 34 wherein n is 2, p is 1, and the compound is N-4-[[3-(2-amino-6-oxohydropurin-9-yl) 1-oxopropyl] amino] benzoic acid 1-(dimethylamino)-2-propyl ester.

36. The method of claim 1 wherein A is a substituted or unsubstituted 9-atom bicyclic moiety in which the 5-membered ring has 1 to 3 nitrogen atoms, the

bicyclic moiety having the structure of formula (X)



where:

(a) if the bond between N_1 and the bond between C_5 is a single bond, then the bond between C_6 and R_6 is a double bond, R_6 is O or S, and R_1 is hydrogen, alkyl, aralkyl, cycloalkyl, or heteroaralkyl;

(b) if the bond between N_1 and C_6 is a double bond, then the bond between C_6 and R_6 is a single bond, R_1 is not present, and R_6 is hydrogen, halo, amino, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(c) if the bond between C_2 and N_3 is a single bond, then the bond between C_2 and R_2 is a double bond, R_2 is O or S, and R_3 is hydrogen or alkyl;

(d) if the bond between C_2 and N_3 is a double bond, then the bond between C_2 is a single bond, R_3 is not present, and R_2 is hydrogen, alkyl, aralkyl, cycloalkyl, heteroaralkyl, halo, amino, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1,

where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(e) A_7 and A_8 are C or N;

(i) if A_7 and A_8 are both C and the bond between A_7 and A_8 is a single bond, then the bond between A_8 and R_8 is two single bonds to two hydrogen atoms or is a double bond in which R_8 is O or S and R_7 is two hydrogen atoms;

(ii) if A_7 and A_8 are both C and the bond between A_7 and A_8 is a double bond, then R_7 is hydrogen, the bond between A_8 and R_8 is a single bond and R_8 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(iii) if A_7 and A_8 are both N, then the bond between A_7 and A_8 is a double bond, and R_7 and R_8 are not present;

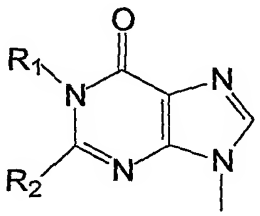
(iv) if A_7 is C and A_8 is N, then the bond between A_7 and A_8 is a double bond, R_7 is hydrogen, and R_8 is not present;

(v) if A_7 is N, A_8 is C, and the bond between A_7 and A_8 is a double bond, then R_7 is not present, the bond between A_8 is a single bond, and R_8 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(vi) if A_7 is N, A_8 is C, and the bond between A_7 and A_8 is a single bond, then R_7 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, the bond between A_8 and R_8 is a double bond, and R_8 is O or S; and

(f) N_9 is bonded to L; with the proviso that A does not have the structure of an unsubstituted guanine or hypoxanthine.

37. The method of claim 3 wherein the purine moiety is a purine moiety of formula (XI)



in which:

(a) R_1 is selected from the group consisting of hydrogen, alkyl, aralkyl, cycloalkyl, and heteroaralkyl; and R_2 is selected from the group consisting of hydrogen, alkyl, aralkyl, cycloalkyl, heteroaralkyl, halo, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, arylkoxycarbonyl, heteroarylokoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroarylkylaminocarbonyl in which the alkyl portions could be cyclic and can contain from one to three heteroatoms which could be N, O, or S, with the proviso that both R_1 and R_2 are not hydrogen and that R_1 is not hydrogen when R_2 is amino.

38. The method of claim 37 wherein R_1 is butyl and R_2 is hydrogen.

39. The method of claim 37 wherein R_1 is benzyl and R_2 is hydrogen.

40. The method of claim 37 wherein R_1 is dimethylaminoethyl and R_2 is hydrogen.

41. The method of claim 37 wherein R_1 is cyclopentyl and R_2 is hydrogen.

42. The method of claim 37 wherein R_1 is cyclohexylmethyl and R_2 is hydrogen.

43. The method of claim 37 wherein R_1 is cyclopropylmethyl and R_2 is hydrogen.

44. The method of claim 37 wherein R_1 is hydrogen and R_2 is phenyl.

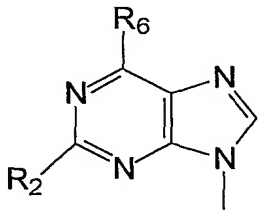
45. The method of claim 37 wherein R_1 is hydrogen and R_2 is butyl.

46. The method of claim 37 wherein R_1 is butyl and R_2 is butyl.

47. The method of claim 37 wherein R_1 is hydrogen and R_2 is methyl.

48. The method of claim 37 wherein R_1 is hydrogen and R_2 is phenylamino.

49. The method of claim 3 wherein the purine moiety is a purine moiety of Formula (XII)



in which:

(a) R_2 is selected from the group consisting of hydrogen, halo, amino, OQ_3, SQ_3, $NHNH_2$, $NHOQ_3$, NQ_3Q_4, or NHQ_3, where Q_3 and Q_4 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, and heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_3 and Q_4 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_3 where Y_3 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S; and

(b) R_6 is selected from the group consisting of hydrogen, halo, amino, OQ_5, SQ_5, $NHNH_2$, $NHOQ_5$, NQ_5Q_6, or NHQ_6, where Q_5 and Q_6 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, and heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_5 and Q_6 are present together and are alkyl, they can be taken together to form a 5- or 6- membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, arylkoxycarbonyl, heteroarylkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S.

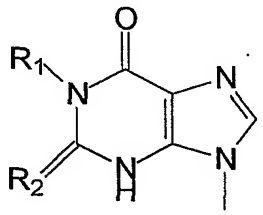
50. The method of claim 49 wherein R_2 is hydrogen and R_6 is amino.

51. The method of claim 49 wherein R_6 is chloro.

52. The method of claim 49 wherein R_6 is phenylamino.

53. The method of claim 49 wherein R_2 is amino and R_6 is chloro.

54. The method of claim 3 wherein the purine moiety is a purine moiety of Formula (XIII)



in which:

(a) R_1 is hydrogen, alkyl, aralkyl, cycloalkyl, or heteroaralkyl; and

(b) R_2 is O or S.

55. The method of claim 54 wherein R_1 is hydrogen.

56. The method of claim 54 wherein R_2 is O.

57. The method of claim 54 wherein R_2 is S.

58. The method of claim 3 wherein the compound is 4-[3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)propionylamino] benzoic acid ethyl ester.

59. The method of claim 3 wherein the compound is 4-[3-(1-butyl-6-oxo-1,6-dihydropurin-9-yl)propionylamino] benzoic acid ethyl ester.

60. The method of claim 3 wherein the compound is 4-[3-(1-methyl-6-oxo-1,6-dihydropurin-9-yl)propionylamino] benzoic acid ethyl ester.

61 The method of claim 3 wherein the compound is 4-[3-(1-2-dimethylaminoethyl)-6-oxo-1,6-dihydropurin-9-yl) propionylamino] benzoic acid ethyl ester.

62. The method of claim 3 wherein the compound is 4-[3-(2,6-dioxo-1,2,3,6-tetrahydropurin-9-yl) propionylamino] benzoic acid ethyl ester.

63. The method of claim 3 wherein the compound is 4-[3-(6-methoxypurin-9-yl) propionylamino] benzoic acid ethyl ester.

64. The method of claim 3 wherein the compound is 4-[3-(6-dimethylaminopurin-9-yl) propionylamino] benzoic acid ethyl ester.

65. The method of claim 3 wherein the compound is 4-[3-(2-amino-6-chloropurin-9-yl) propionylamino] benzoic acid ethyl ester.

66. The method of claim 3 wherein the compound is 4-[2-(6-oxo-2-thioxo-1,2,3,6-tetrahydropurin-9-yl) propionylamino] benzoic acid ethyl ester.

67. The method of claim 3 wherein the compound is 4-[2-(2-butyl-6-oxo-1,6-dihydropurin-9-yl) propionylamino] benzoic acid ethyl ester.

68. The method of claim 3 wherein the compound is 4-[2-(6-oxo-2-phenyl-1,6-dihydropurin-9-yl) propionylamino] benzoic acid ethyl ester.

69. The method of claim 3 wherein the compound is 4-{[3-(6-chloropurin-9-yl) propionyl] methylamino} benzoic acid methyl ester.

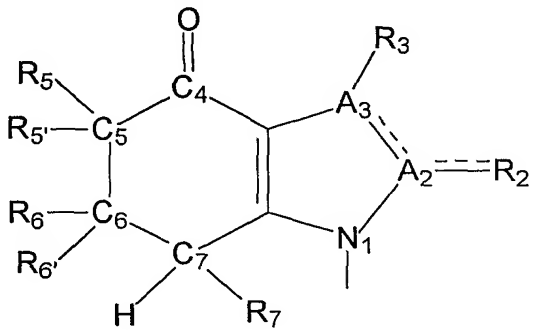
70. The method of claim 3 wherein the compound is 3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)-N-[3-(2-oxopyrrolidin-1-yl)propyl] propanamide.

71. The method of claim 3 wherein the compound is 3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)-N-{2-[2-(2-oxopyrrolidin-1-yl)acetylamino]ethyl} propanamide.

72. The method of claim 3 wherein the compound is N-[3-(2-oxopyrrolidin-1-yl)propyl]-3-(6-oxo-2-thioxo-1,2,3,6-tetrahydropurin-9-yl) propanamide.

73. The method of claim 3 wherein the compound is 3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)-N-(3-morpholin-4-yl)propyl propionamide.

74. The method of claim 1 wherein the compound is a tetrahydroindolone derivative or analogue where A is a 9-atom bicyclic moiety in which the 5-membered ring has one to three nitrogen atoms, the bicyclic moiety of Formula (XIV)



where:

(a) N_1 is bonded to L;

(b) A_2 and A_3 are C or N;

(i) If A_2 and A_3 are both C and the bond between A_2 and A_3 is a single bond, then the bond between A_2 and R_2 is two single bonds, two hydrogen atoms or is a double bond in which R_2 is O or S and R_3 is two hydrogen atoms;

(ii) If A_2 and A_3 are both C and the bond between A_2 and A_3 is a double bond, then R_3 is hydrogen, the bond between A_2 and R_2 is a single bond and R_2 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(iii) If A_2 and A_3 are both N, then the bond between A_2 and A_3 is a double bond and R_2 and R_3 are not present;

(iv) If A_2 is N and A_3 is C, then the bond between A_2 and A_3 is a double bond, R_2 is not present, and R_3 is hydrogen;

(v) If A_2 is C, A_3 is N, and the bond between A_2 and A_3 is a double bond, then R_3 is not present, the bond between A_2 and R_2 is a single bond, and R_2 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(vi) If A_2 is C, A_3 is N, and the bond between A_2 and A_3 is a single bond, then R_3 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, or heteroaralkenyl, the bond between A_2 and R_2 is a double bond, and A_2 is O or S;

(c) R_5 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, NH_2, NHQ_1, NQ_1Q_2, OH, OQ_1, or SQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom, which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(d) $R_{5'}$ is hydrogen unless R_5 is alkyl, in which case R_5 is hydrogen or the same alkyl as R_5;

(e) R_5 and $R_{5'}$ can be taken together as a double bond to C_5, and can be O, S, NQ_3, or C which can be substituted with one or two groups R_5, where Q_3 is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(f) R_6 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, NH_2, NHQ_4, NQ_4Q_5, OH, OQ_4, or SQ_4, where Q_4 and Q_5 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl,

alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_4 and Q_5 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom, which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

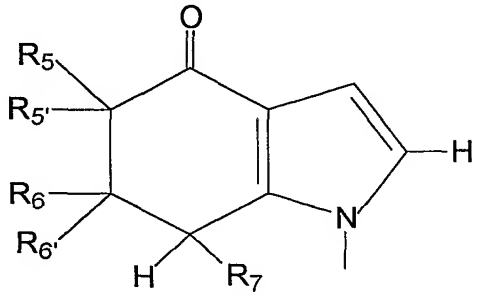
(g) $R_{6'}$ is hydrogen unless R_6 is alkyl, in which case $R_{6'}$ is hydrogen or the same alkyl as R_6;

(h) R_6 and $R_{6'}$ can be taken together as a double bond to C_6 and can be O, S, NQ_6, or C which can be substituted with one or two groups R_5, and where Q_6 is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S; and

(i) R_7 is hydrogen unless R_5 is alkyl and $R_{5'}$ is hydrogen, in which case R_7 is the same alkyl as R_5.

75. The method of claim 74 wherein A is a tetrahydroindolone moiety.

76. The method of claim 75 wherein the tetrahydroindolone moiety is a tetrahydroindolone moiety of Formula (XV)



in which:

(a) R_5 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, NH_2, NH_1, NQ_1Q_2, OH, OQ_1, or SQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl, in which the alkyl portions can be cyclic and can contain from one to three heteroatoms which can be N, O, or S;

(b) $R_{5'}$ is hydrogen;

(c) R_6 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, NH_2, NHW_1, NQ_1Q_2, OH, OQ_1, or SQ_1, where Q_1 and Q_2 are aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl, in which the alkyl portions can be cyclic and can contain from one to three heteroatoms which can be N, O, or S and where W_1 is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from one to three heteroatoms which can be N, O, or S;

(d) $R_{6'}$ is hydrogen; and

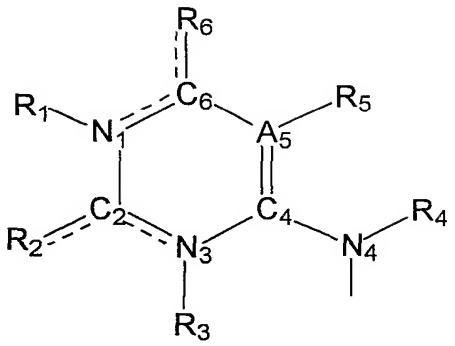
(e) R_7 is hydrogen.

77. The method of claim 76 wherein R_5, $R_{5'}$, R_6, $R_{6'}$, and R_7 are all hydrogen.

78. The method of claim 77 wherein the compound is 4-[3-(4-oxo-4,5,6,7-tetrahydroindolon-1-yl) propionylamino] benzoic acid ethyl ester.

79. The method of claim 77 wherein the compound is 4-[3-(4-oxo-4,5,6,7-tetrahydroindolon-1-yl) propionylamino] benzoic acid.

80. The method of claim 1 wherein A is an amino-substituted 6-membered heterocyclic moiety of Formula (XVI)



where:

(a) if the bond between N_1 and the bond between C_6 is a single bond, then the bond between C_6 and R_6 is a double bond, R_6 is O or S, and R_1 is hydrogen, alkyl, aralkyl, cycloalkyl, or heteroaralkyl;

(b) if the bond between N_1 and C_6 is a double bond, then the bond between C_6 and R_6 is a single bond, R_1 is not present, and R_6 is hydrogen, halo, amino, OH, OQ_1, SQ_1, $NHNH_2$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(c) if the bond between C_2 and N_3 is a single bond, then the bond between C_2 and R_2 is a double bond, R_2 is O or S, and R_3 is hydrogen or alkyl;

(d) if the bond between C_2 and N_3 is a double bond, then the bond between C_2 and R_2 is a single bond, R_3 is not present, and R_2 is hydrogen, alkyl, aralkyl, cycloalkyl, heteroaralkyl, halo, amino, OH, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl,

aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_3, where Y_3 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(e) R_4 is hydrogen, alkyl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl;

(f) A_5 is carbon or nitrogen;

(g) if A_5 is nitrogen, then R_5 is not present;

(h) if A_5 is carbon, then R_5 is hydrogen, amino, alkyl, alkoxy, halo, nitro, aryl, cyano, alkenyl, or alkaryl;

(i) if R_5 and R_6 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S; and

(j) N_4 is bonded to L.

81. The method of claim 80 wherein A_5 is carbon and the 6-membered heterocyclic moiety is a pyrimidine moiety.

82. The method of claim 81 wherein R_2 is O and R_3 is hydrogen.

83. The method of claim 82 wherein the pyrimidine moiety is selected from the group consisting of cytosine, thymine, uracil, 3-methyluracil, 3-methylthymine, 4-methylcytosine, 5-methylcytosine, 5-hydroxymethylcytosine, 5-hydroxyuracil, 5-carboxymethyluracil, and 5-hydroxymethyluracil.

84. The method of claim 81 wherein R_2 is S and R_3 is hydrogen.

85. The method of claim 84 wherein the pyrimidine moiety is selected from the group consisting of 2-thiouracil, 5-methylamino-2-thiouracil, 5-methyl-2-thiouracil, 2-thiocytosine.

86. The method of claim 81 wherein R_2 is amino and the bond between C_2 and N_3 is a double bond.

87. The method of claim 86 wherein the pyrimidine moiety is selected from the group consisting of 2-aminopyrimidinone and 2-amino-4-chloropyrimidine.

88. The method of claim 81 wherein R_2 is hydrogen and the bond between C_2 and N_3 is a double bond.

89. The method of claim 88 wherein the pyrimidine moiety is selected from the group consisting of 4-chloropyrimidine, 5-amino-4-chloropyrimidine, 4-chloro-5-methylpyrimidine, 4-chloro-5-hydroxymethylpyrimidine, and 4-chloro-5-carboxymethylpyrimidine.

90. The method of claim 81 wherein R_1 is hydrogen, methyl, or ethyl, R_5 is hydrogen, methyl, or ethyl, and R_6 is O.

91. The method of claim 90 wherein the pyrimidine moiety is pyrimidinone.

92. The method of claim 81 wherein the compound is 4-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester.

93. The method of claim 81 wherein the compound is 4-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester.

94. The method of claim 81 wherein the compound is 4-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester.

95. The method of claim 81 wherein the compound is 4-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid.

96. The method of claim 81 wherein the compound is 4-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid.

97. The method of claim 81 wherein the compound is 4-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid.

98. The method of claim 81 wherein the compound is 3-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester.

99. The method of claim 81 wherein the compound is 3-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester.

100. The method of claim 81 wherein the compound is 3-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester.

101. The method of claim 81 wherein the compound is 3-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid.

102. The method of claim 81 wherein the compound is 3-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid.

103. The method of claim 81 wherein the compound is 3-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid.

104. The method of claim 1 wherein L has the structure $-(CH_2)_n-$ wherein n is an integer from 1 to 6.

105. The method of claim 104 wherein n is 2.

106. The method of claim 104 wherein n is 3.

107. The method of claim 1 wherein the moiety B is –OZ.

108. The method of claim 107 wherein Z is hydrogen.

109. The method of claim 107 wherein Z is alkyl.

110. The method of claim 109 wherein Z is selected from the group consisting of methyl, ethyl, butyl, propyl, and isopropyl.

111. The method of claim 1 wherein B is $-N(Y_1)-D$.

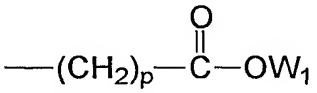
112. The method of claim 111 wherein Y_1 is hydrogen.

113. The method of claim 111 wherein Y_1 is lower alkyl.

114. The method of claim 113 wherein Y_1 is methyl.

115. The method of claim 111 wherein D is a moiety having at least one polar, charged, or hydrogen-bond-forming group to increase the water-solubility of the compound.

116. The method of claim 115 wherein D is a carboxylic acid or carboxylic acid ester with the structure

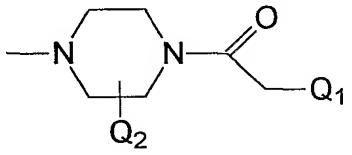


wherein p is an integer from 1 to 6 and W_1 is selected from the group consisting of hydrogen and lower alkyl.

117. The method of claim 116 wherein W_1 is hydrogen.

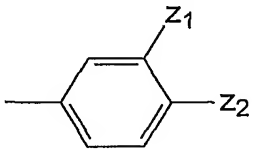
118. The method of claim 116 wherein W_1 is ethyl.

119. The method of claim 115 wherein D and Y_1 are taken together to form a piperazine derivative of the structure



wherein Q_1 is hydrogen, methyl, ethyl, butyl, or propyl, and Q_2 is hydrogen or methyl, where, if Q_2 is methyl, it can be located on either of the two possible positions in the piperazine ring.

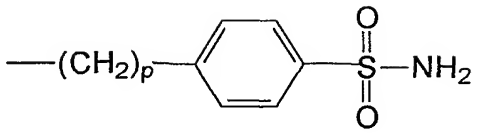
120. The method of claim 115 wherein D has the structure



wherein one of Z_1 and Z_2 is hydrogen and the other is Z_1 and Z_2 is –COOH or –$COOW_1$, wherein W_1 is alkyl.

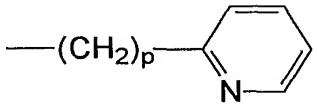
121. The method of claim 120 wherein W_1 is selected from the group consisting of methyl, ethyl, propyl, butyl, and isobutyl.

122. The method of claim 115 wherein D is a phenylsulfonamidyl moiety of the structure



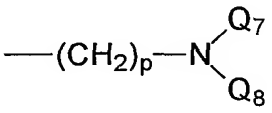
wherein p is an integer from 0 to 6.

123. The method of claim 115 wherein D is an alkylpyridyl moiety of the structure



wherein p is an integer from 1 to 6.

124. The method of claim 114 wherein D is an dialkylaminoalkyl moiety of the structure



wherein p is an integer from 1 to 6 and Q_7 and Q_8 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_7 and Q_8 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S.

125. The method of claim 124 wherein Q_7 and Q_8 are each alkyl.

126. The method of claim 125 wherein Q_7 and Q_8 are each selected from the group consisting of methyl, ethyl, propyl, butyl, and isobutyl.

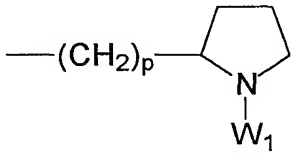
127. The method of claim 126 wherein Q_7 and Q_8 are taken together to form 5- or 6-membered optionally substituted ring.

128. The method of claim 127 wherein the ring is a morpholinyl ring.

129. The method of claim 127 wherein the ring is a pyrrolidinyl ring that is optionally substituted with oxo.

130. The method of claim 126 wherein the ring is a piperidinyl ring that is optionally substituted with methyl or ethyl.

131. The method of claim 115 wherein D is an alkylpyrrolidinyl moiety of the structure



wherein p is an integer from 1 to 6 and W_1 is selected from the group consisting of methyl, ethyl, and propyl.

132. The method of claim 1 wherein the compound has a log P of from about 1 to about 4.

133. The method of claim 1 wherein the action of the compound having activity against disease-induced neuropathy is to induce upregulation of neurotrophic factor synthesis.

134. The method of claim 133 wherein the neurotrophic factor is selected from the group consisting of NGF, NT-3, BDNF, and NT-4/5.

135. The method of claim 1 wherein the administration of the compound having activity against disease-induced neuropathy induces peripheral nerve sprouting in the skin of the patient to whom the compound was administered.

136. The method of claim 135 wherein the peripheral nerve sprouting is nociceptive nerve sprouting.

137. The method of claim 136 wherein the nociceptive nerve sprouting is induced without the occurrence of hyperalgesia.

138. The method of claim 1 wherein the disease-induced peripheral neuropathy is diabetic neuropathy.

139. The method of claim 138 wherein the administration of the compound having activity against diabetic neuropathy prevents large and small sensory nerve dysfunction.

140. The method of claim 1 wherein the peripheral neuropathy is caused by a condition other than diabetic neuropathy.

141. The method of claim 140 wherein the disease-induced peripheral neuropathy is caused by a condition selected from the group consisting of acromegaly, hypothyroidism, AIDS, leprosy, Lyme disease, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, periarteritis nodosa, Wegener's granulomatosis, cranial arteritis, and sarcoidosis.

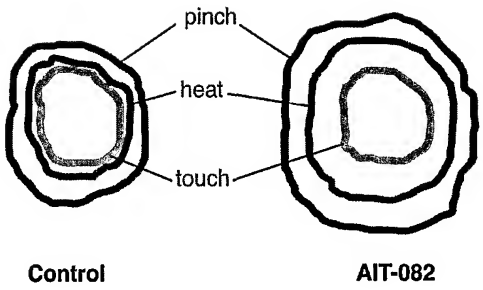

pinch
heat
touch
Control
AIT-082

FIG. 1A

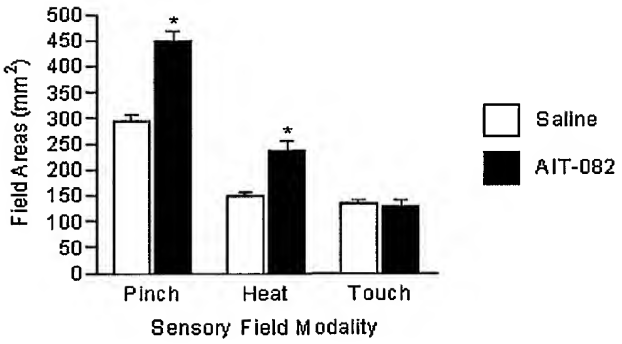

Field Areas (mm2)
500
450
400
350
300
250
200
150
100
50
0
*
*
Pinch
Heat
Touch
Sensory Field Modality
Saline
AIT-082

FIG. 1B

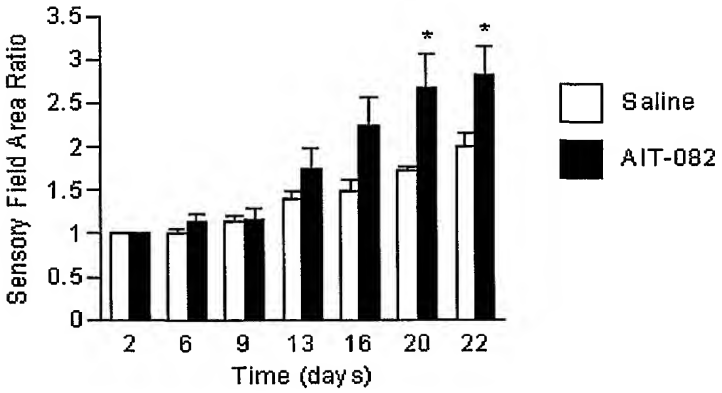

Sensory Field Area Ratio
3.5
3
2.5
2
1.5
1
0.5
0
2
6
9
13
16
20
22
Time (days)
*
*
Saline
AIT-082

Fig. 2A

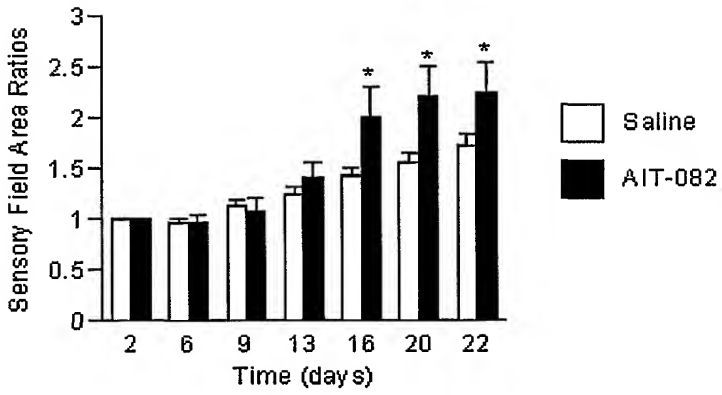

Sensory Field Area Ratios
3
2.5
2
1.5
1
0.5
0
2
6
9
13
16
20
22
Time (days)
*
*
*
Saline
AIT-082

Fig. 2B

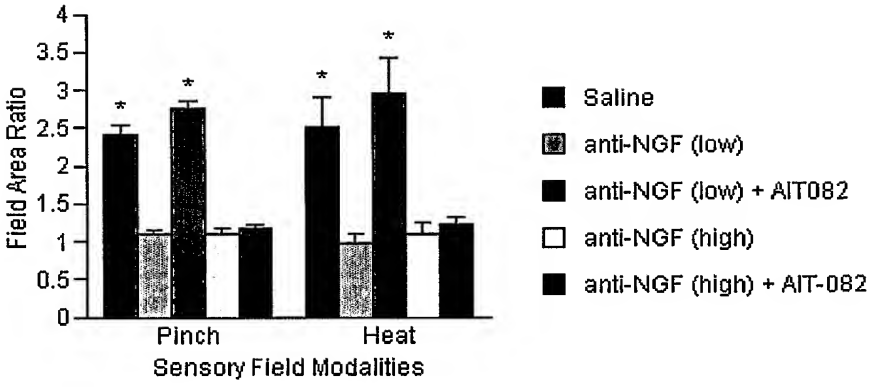

Field Area Ratio
4
3.5
3
2.5
2
1.5
1
0.5
0
*
*
*
*
Pinch
Heat
Sensory Field Modalities
Saline
anti-NGF (low)
anti-NGF (low) + AIT082
anti-NGF (high)
anti-NGF (high) + AIT-082

FIG.3

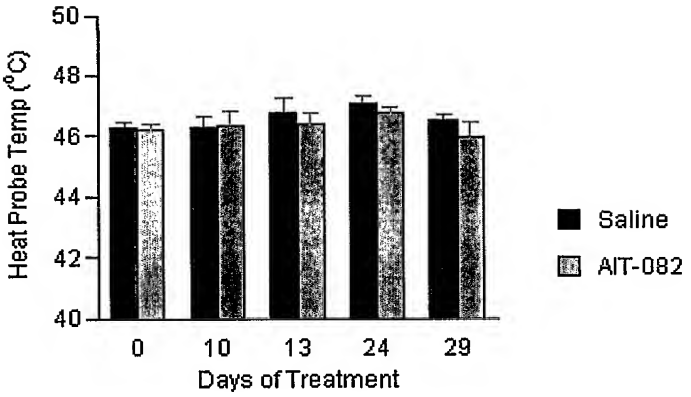


FIG. 4A

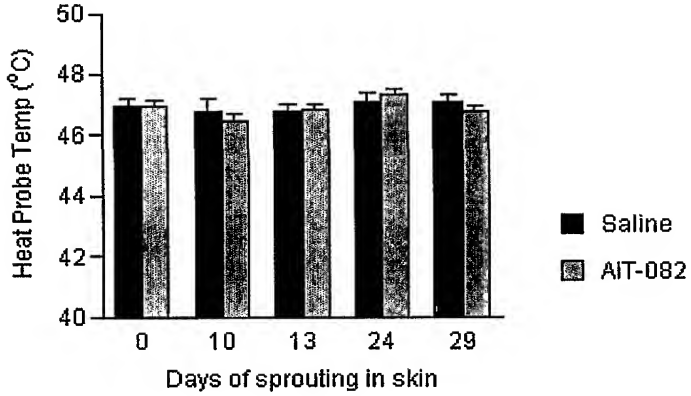


FIG. 4B

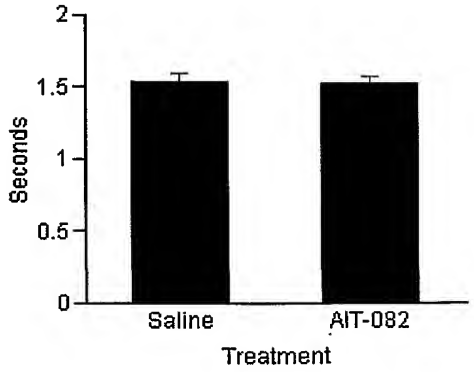


FIG. 4C

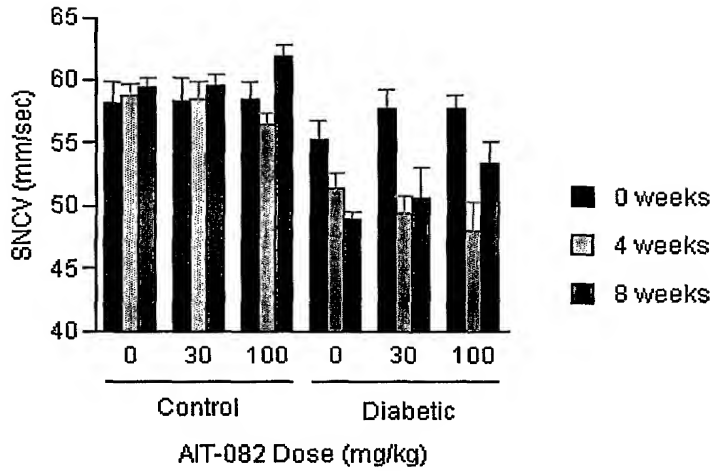

SNCV (mm/sec)
65
60
55
50
45
40
0
30
100
0
30
100
Control
Diabetic
AIT-082 Dose (mg/kg)
0 weeks
4 weeks
8 weeks

FIG. 5

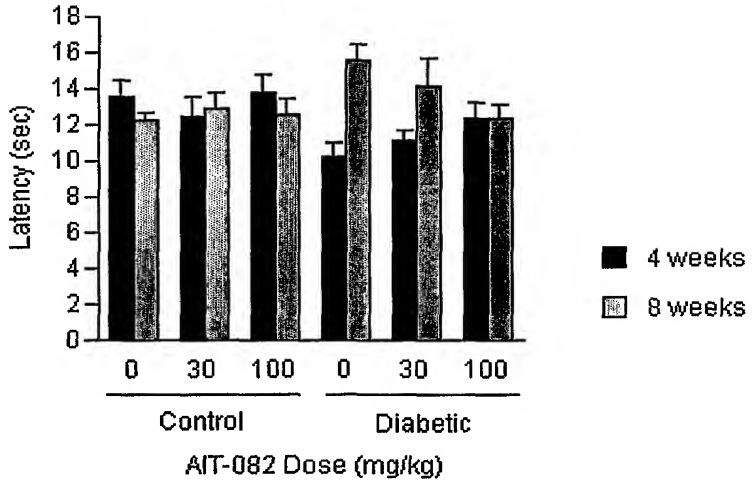

Latency (sec)
18
16
14
12
10
8
6
4
2
0
0
30
100
0
30
100
Control
Diabetic
AIT-082 Dose (mg/kg)
4 weeks
8 weeks

FIG. 6

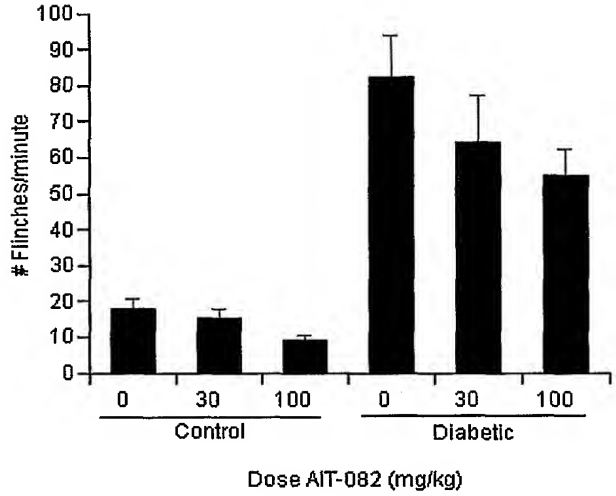

Flinches/minute
100
90
80
70
60
50
40
30
20
10
0
0
30
100
0
30
100
Control
Diabetic
Dose AIT-082 (mg/kg)

FIG. 7

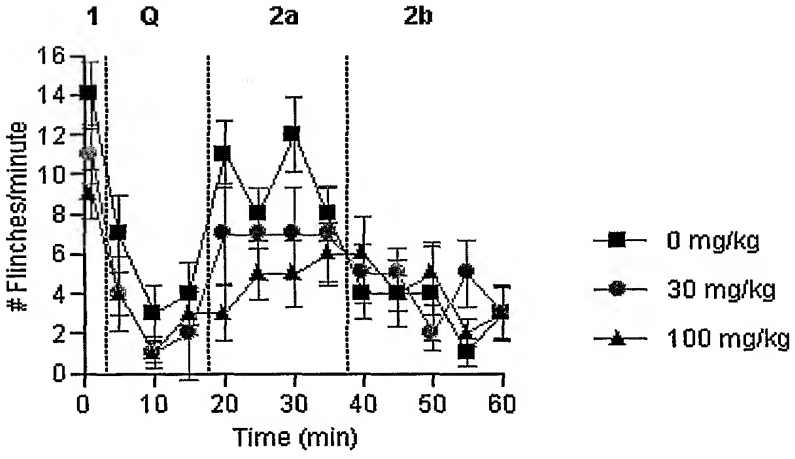

1
Q
2a
2b
Flinches/minute
16
14
12
10
8
6
4
2
0
0
10
20
30
40
50
60
Time (min)
0 mg/kg
30 mg/kg
100 mg/kg

FIG. 8

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 January 2002 (17.01.2002)

PCT

(10) International Publication Number
WO 02/004452 A3

(51) International Patent Classification[7]: A61K 31/52, 31/405, 31/505

(21) International Application Number: PCT/US01/21526

(22) International Filing Date: 6 July 2001 (06.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/216,844 7 July 2000 (07.07.2000) US

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(72) Inventors; and

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(74) Agents: **CULLMAN, Louis, C.** et al.; Oppenheimer Wolff & Donnelly LLP, Suite 700, 840 Newport Center Drive, Newport Beach, CA 92660 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
3 January 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/004452 A3

(54) Title: METHODS FOR TREATMENT OF DISEASE-INDUCED PERIPHERAL NEUROPATHY AND RELATED CONDITIONS

(57) Abstract: A method of treating disease-induced peripheral neuropathy comprises administering to a patient with disease-induced peripheral neuropathy an effective quantity of a purine derivative or analogue, a tetrahydroindolone derivative or analogue, or a pyrimidine derivative or analogue. If the compound is a purine derivative, the purine moiety can be guanine or hypoxanthine. The compound can induce peripheral nerve sprouting through the action of a neurotrophic factor such as nerve growth factor (NGF) without the occurrence of hyperalgesia. The peripheral nerve sprouting can be nociceptive nerve sprouting. The disease-induced peripheral neuropathy can be diabetic neuropathy or disease-induced peripheral neuropathy with another basis.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/21526

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/52 A61K31/405 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, BEILSTEIN Data, BIOSIS, EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 03125 A (A.J. GLASKY) 8 February 1996 (1996-02-08) page 19, line 26 - page 20, line 9; examples 2, 12, 29; claims 15, 16 and 31	1-4,6-9, 111,112, 115,120, 133,134
Y	idem	1-15, 107-116, 120-131, 133,134, 138-141

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 May 2002	9. 08. 2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Amsterdam, L

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/US 01/21526

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 91 14434 A (A.J. GLASKY) 3 October 1991 (1991-10-03) page 7, lines 30-35; page 42, lines 15-18; pages 44-59	1-15, 107-116, 120-131
A	idem	36,37

Y	WO 97 33572 A (SOMERSET PHARMACEUTICALS INC) 18 September 1997 (1997-09-18) page 5, line 16 - page 7, line 16	1,133, 134, 138-141

A	M.P. RATHBONE ET AL: DRUG DEVELOPMENT RESEARCH, vol. 45, no. 3-4, 1998, pages 356-372, XP000904784 page 363, column 1, lines 26-29; page 367, column 2, line 36 - page 368, column 1, line 42	1-4,6-9, 111,112, 115,120, 133-137

A	B.R. BAKER ET AL: J. PHARM. SCI., vol. 54, no. 11, 1965, pages 1609-1616, XP001076681 table I, compounds XV, XVIII; scheme I, compounds XVI, XXII-XXVII, XXIX	1,3,36, 49-51, 107,108, 111,112, 115-117, 120,121

A	B.R. BAKER ET AL: J. PHARM. SCI., vol. 54, no. 12, 1965, pages 1774-1781, XP001076680 table 1, compounds VIII, XXVI, XXVII	1,3,36, 107,108, 111,112, 115,120

A	WO 96 20711 A (UNIVERSITY OF MASSACHUSETTS MEDICAL CENTER) 11 July 1996 (1996-07-11) page 3, lines 1-23; page 4, lines 14-29; page 5, line 25; page 8, lines 24-32	1,3,16, 36,37, 48,107, 108

P,X	M. HOLMES ET AL: SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 26, no. 1-2, 2000, XP001040388 abstract no. 511.9	1-4,6-9, 111,112, 115,120, 133-137
P,O, X	& 30th Annual Meeting of the Society of Neuroscience; New Orleans, US; November 04-09 2000	

	-/--	

INTERNATIONAL SEARCH REPORT

Inte ıal Application No
PCT/US 01/21526

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 29039 A (NEOTHERAPEUTICS INC) 26 April 2001 (2001-04-26) whole document, in particular formulae I-VII, X, XIII-XIV, XVIII, XXVI-XXVII, XXX, XXXII, XXXV, XL, and page 31, line 26 - page 32, line 13	1-3, 16-35, 107,108, 111,112, 115-117, 120-131, 133,134
A	idem	36,37

P,A	WO 00 32197 A (ALCON LABORATORIES INC) 8 June 2000 (2000-06-08) page 7; claims 1-3, 8-10	1-4,6-9, 111,112, 115,120, 133,134

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 01/21526

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-141 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-2, 104-141 (in part); 3-73

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-2, 104-141 (in part); 3-73

   Compounds of the formula A-L-B of claim 1, wherein A is selected from the group consisting of a purine moiety and a purine analogue, for use in treating peripheral neuropathy.

2. Claims: 1-2, 104-141 (in part); 74-79

   Compounds of the formula A-L-B of claim 1, wherein A is selected from the group consisting of a tetrahydroindolone moiety and a tetrahydroindolone analogue, for use in treating peripheral neuropathy.

3. Claims: 1-2, 104-141 (in part); 80-103

   Compounds of the formula A-L-B of claim 1, wherein A is selected from the group consisting of a pyrimidine moiety and a pyrimidine analogue, for use in treating peripheral neuropathy.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1 and 36 relate to extremely large numbers of possible compounds for use in the treatment of peripheral neuropathy. In fact, the claims contain so many variables and options that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be sufficiently clear and concise, namely those parts relating to compounds of formula A-L-B of claim 1, wherein

A is a substituted or unsubstituted purine moiety covered by formula X of claim 36 for A7 is N and A8 is C and having any of the structures of formulae XI, XII or XIII (see claims 37, 49 or 54, respectively), an unsubstituted hypoxanthine moiety (see claim 4) or an unsubstituted guanine moiety (see claim 16),

L is a -(C1-6 straight or branched chain alkylene)-C(O)- linking group (see claims 6, 12, 14, 18, 22, 25, 28, 30, 34, 58-73) attached to N) of the purine, hypoxanthine or guanine moiety (see claim 36, page 42, (f)), and

B is -OZ wherein Z is hydrogen or alkyl (see claims 108-110), or -N(Y1)-D wherein Y1 is hydrogen or alkyl (see claims 112-114) and D is as defined in claims 116-131 or is any of the D groups present in the compounds of claims 6, 12, 14, 18, 22, 25, 28, 30, 34, 58-73.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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